EXCITABILITY
OF THE
HEART

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Chandler McC Brooks Ph D , Brian F Hoffman, M D , E E Suckling, M Sc , M E E , Department of Physiology and Pharmacology State University of New York College of Medicine at New York City

and

Oscar Orias M D , Instituto de Investigacion Medica Mercedes y Martin Ferreyra Cordoba Argentina

with a Foreword by

Carl J Wiggers, M D



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Preface

THIS MONOGRAPH has been written to record the results and conclusions obtained from a study of the changes in excitability of the heart throughout its cycle Experiments to be described herein were begun in 1948 while Dr Oscar Orias was associated with us as Visiting Professor of Physiology in what was then the Long Island College of Medicine.

A field of common interest to our department and to Dr Orias was cardiac excitability Consequently it was decided to restudy with more adequate instrumentation than had hitherto been employed, the changes in excitability which occur during the cardiac cycle Our preliminary experiments revealed previously unrecognized phenomena and the methods devised provided a means of studying them During the intervening years many of the projects thought of initially have been brought to conclusion and new problems encountered as a result of work done in this laboratory When circumstances again permitted Dr Orias to visit our institution now a part of the State University of New York, we felt this to be a propitious time for summarizing our accomplishments and for review of the possible directions of future endeavors

The common theme of all sections of this monograph is Cardiac Excitability but each chapter has been written as an independent unit. The various sections are complementary rather than interdependent. This plan has required some repetition of material but we believe it will enhance the usefulness of this book to the student and the practitioner of medicine. An attempt has also been made to introduce each subject by presenting basic concepts and information in a very simple fashion in order to equip the reader to deal with the complexities of recent advances in the various fields considered

Although this monograph was written by the authors mentioned, other members of the department participated in the experiments described in its chapters We wish to acknowledge the contributions of Julius Belford Fred F Kao Jerome L. Gilbert, James O Pinkston, Arthur A. Siebens and others who have worked with us upon this project. Dr Jerome L. Gilbert of this institution and Dr Silvio Weidmann of the Physiological Institute, University of Berne Switzerland read our manuscripts and offered numerous suggestions from which we profited greatly Dr Paul F Cranefield in addition to giving significant assistance in the preparation of the chapter on excitability served as a consultant with respect to matters of historical interest. Dr Siebens also aided us in the preparation of the chapter dealing with mechanical responses of the heart. We like

Foreword

PROGRESS IN BASIC RESEARCH and in its practical application rests chiefly on the development of new tools for digging out nature's secrets

As early as 1850, Schiff showed that the heart does not respond to mechanical excitation applied in certain phases of the cardiac cycle It required the invention of the inductorium before Kronecker and Marey, some twenty five years later, were able to define the refractory period of the heart more exactly Another fifty years elapsed before sufficient technical advances had been made for the discovery that the mammalian ventricle responds to strong electric shocks during late systole by one or several premature contractions, and that these are often followed by ventricular fibrillation This phase of the cardiac cycle was, therefore, called the vulnerable period During the years 1939-42 Rene Wegria, A Sidney Harris, Gordon Moe and I studied the mechanisms initiating fibrillation and, because of such information, we were able to improve on procedures for defibrillating the ventricles Again, it was necessary to discontinue researches before solutions to many problems could be realized, because suitable methods were not available

Meanwhile great strides had been made in the study of the excitability of nerves by newly developed techniques and apparatus Since Chandler McC Brooks had been trained in the new methodology and Oscar Orias, of Cordoba, Argentina, was a master of experimentation on mammalian hearts, they combined their talents in 1948 and thoroughly restudied cardiac excitability by modern methods This collaboration resulted in a brilliant series of papers, published chiefly in the American Journal of Physiology

It seemed almost an obligation for them to reanalyze their important discoveries in relation to other basic discoveries of recent date, so that others not too deeply versed in the intricacies of this special field might be enlightened Hence, this monograph

After the manuscript had been essentially finished Oscar Orias passed away quite suddenly as a result of coronary thrombosis To me, this monograph will represent a memorial to a formal pupil, an esteemed investigator and a sincere friend

The monograph will, I predict, be considered a classic by physiologists It should likewise appeal to progressive physicians and surgeons for in the present era, it is not sufficient that one be trained in the proper use of drugs and procedures, one must also understand the conditions to be treated

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CARL J WIGGERS, M D

1 Historical Synopsis and Definition of the Scope of This Work

A preliminary review is given of the early studies of cardiac excitability and response A summary of the purposes of this monograph and an estimation of the need for new information based on the present state of our knowledge of cardiac physiology is presented

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HISTORICAL SYNOPSIS

THE FIRST IMPORTANT STUDY of cardiac excitability was that started by Bowditch in 1871 while working in Carl Ludwig s laboratory at Leipzig Long before this time however William Harvey (1628) Stephen Hales (1733) and others (see Rothschuh, 1952) had determined the nature of the function of the heart and had learned much about the properties of this organ. However a great deal was known about the irritability of tissues the excitatory process and the conduction of excitation before any significant studies of cardiac tissue and their peculiarities were begun (see Chapter 2)

Bowditch (1871) reported that the frog s heart did not respond in the same fashion as did skeletal muscle to repeated electrical stimulation in that there was not always a one to one ratio between the number of stimuli given and the number of contractions elicited When a total of 100 successive stimuli were applied to the heart the proportion of evoked contractions increased as the interval between the stimuli was prolonged It thus became apparent that the frog heart required a longer time for recovery between contractions than did frog skeletal muscle Bowditch offered two suggestions as possible explanations of this greater irregularity of response in heart muscle first, that exhaustion rendered the heart incapable of response to all stimuli of a series and second that inhibitory nerves were activated by the more rapid stimulation and depressed the irritability of the heart tissue It would seem that he failed to see any connection between this phenomenon and the length of the cardiac cycle itself

Five years later applying an improved technique for recording the

wise are much indebted to Mrs Louise H Ray for preparing all the illustrations used in this monograph and to Mrs Ruth Danziger and Mrs Margaret McHugh for the assistance they rendered in the preparation of typescripts

The original work reported here was supported in part by grants from the Life Insurance Medical Research Fund and from the New York Heart Association We wish to take this opportunity to express our gratitude for the encouragement and advisory help we have always received from Dr Francis R Dieuaide and other administrators of the Life Insurance Medical Research Fund and from Dr D F Milam and his associates of the New York Heart Association We have been enabled to publish this monograph because of a grant in support of teaching pertinent to cardiovascular disease from the United States Public Health Service to Dr William Dock This latter grant also enabled Dr Orias to again visit this Institution in 1954 as a consultant participating in the development of our teaching and research enterprises

The untimely death of Dr Oscar Orias occurred before this work was completed The members of this department will ever remember his kindness and his unfailing devotion to the ideals of free men and science All future work done here will rest upon a foundation which was built with his assistance He helped us when we most needed help and this we shall always hold in memory

CHANDLER McC BROOKS, PH D
BRIAN F HOFFMAN M D
E E SUCKLING, M Sc , M E E.

July 1955

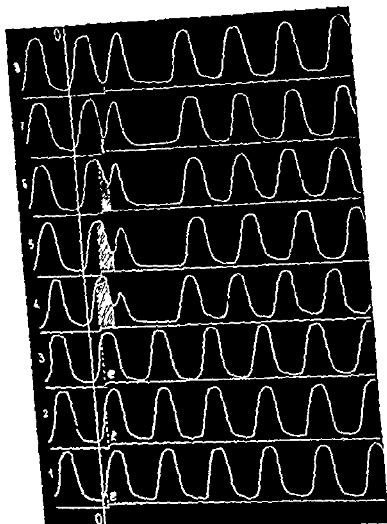


FIGURE 1 Tracings of spontaneous and induced contractions of frog's ventricle showing refractory periods, latency of evoked responses, and the compensatory pause (from Marey 1876) Lower line shows time of stimulation e—ineffective stimulus indicating absolute refractoriness. Line o——o shows onset of spontaneous beats Duration of cross hatched area indicates latency of evoked responses.

movements of the frog's heart, Marey (1876) made a discovery which better explained Bowditch's observation that the heart responded irregularly to high frequencies of stimulation He found that a spontaneous or induced contraction of the heart temporarily reduced its irritability By using an induction coil and sending to the heart only break shocks, he stimulated the ventricle at different intervals following the beginning of naturally occurring systoles Figure 1, which reproduces the records obtained in one of Marey's experiments, shows his results if a stimulus reached the heart early in systole, no response was elicited (records 1, 2 and 3), if the interval between the initiation of systole and the arrival of the stimulus was progressively increased there came a time when a response was evoked but only after a long latency This latency of response varied inversely with the delay of application of the stimulus after the beginning of systole (records 4 to 7) finally, when the stimulus reached the heart during diastole (after complete relaxation) the response never failed to occur and began with minimal latency (record 8) Marey concluded from these experiments that the heart was refractory (inexcitable) during the initial moments of systole These same experiments delineated the irresponsive period which was described later by others

According to Hoff (1942), Fontana (1785) was the first to suggest the general concept of a refractory period His observations on frogs, cats and young lambs led him to conclude that the heart does not contract immediately after relaxation because it does not recover its normal irritability until later Schiff (1850) also studied the changes in irritability of the heart during phases of contraction and he seems to have been the first to use the term "refractory" in referring to the heart s periodic inexcitability Undoubtedly Marey had clearly demonstrated this important property of the myocardial fiber, correctly pointing out that the periodic refractoriness of the heart not only explained the observations of Bowditch, already referred to, but also the well known inability of repetitive stimuli which tetanize skeletal muscle to maintain a heart in the completely contracted state Marey also saw in his experiments that the length of the refractory period was shorter if stronger stimuli were applied If sufficiently strong shocks were used, the refractory period appeared to be abolished When Marey made his observations on the heart the refractory period of skeletal muscle had not yet been discovered but he suggested that investigators should be aware of the possibility of its existence

The extreme latency of the contractions produced by stimuli applied

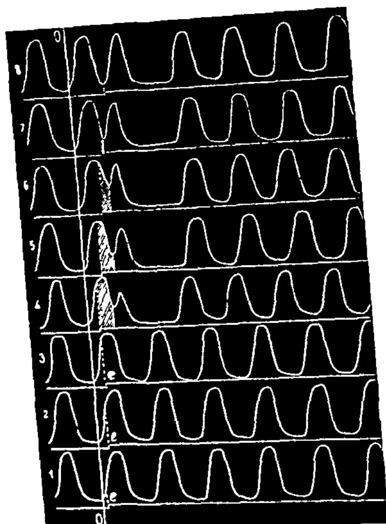


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during the early phases of systole led various individuals to question the validity of Marey's conclusions Hildebrand (1877) suggested that the extra contraction which followed a strong stimulus applied to the ventricle during systole was not a direct response of the ventricle but was due to a leakage of stimulus current to the auricle Since the auricle is in diastole *during the late phases of ventricular systole, it should be more excitable* than the ventricle and stimulation of the auricle would ultimately produce a ventricular response On reinvestigating the matter, Englemann (1895) and Woodworth (1902) satisfied themselves as to the validity of *Hildebrand's objections and discarded the possibility of stimulation of* the ventricle throughout its systolic phase About this same time the reactions of the mammalian heart had been studied and found to be the same as those reported for the amphibian heart It was found, however that *although the ventricle was refractory early in systole, it could be excited* by very strong stimuli before complete relaxation had occurred and the responses thus evoked did have an abnormally long latency (McWilliam, 1888, Gley, 1889, Cushny and Matthews, 1897) Consequently, at the beginning of the present century the current concepts of the characteristics of cardiac excitability were firmly established (see Schafer, 1900) The myocardium was thought to be completely inexcitable during the phase of active contraction, it began to recover its irritability at the onset of relaxation and during diastole the heart became progressively more and more excitable until a maximum was attained Trendelenburg's (1912) observation that the refractory phase coincided with the action potential provided an additional means of identifying the period of the cycle during which the heart was unresponsive to stimulation

The introduction of chronaxie as a measure of excitability did not fundamentally alter the picture as regards the heart A few more or less isolated determinations were made, but the results did not contribute much to our knowledge of the excitability cycle of the mammalian myocardium (see Fredericq, 1928)

In present day textbook discussions of the cardiac cycle the following states of excitability are usually mentioned 1) an absolute refractory period coinciding with systole or the phase of active contraction, 2) a *relative refractory period during early diastole, and 3) a period of normal* excitability lasting until the next systole Carlson was the first to use the expressions "absolute refractory period' (1906) and relative refractory period" (1907) The existence of a phase of "supernormal' excitability

just after the relative refractory period is sometimes mentioned Adrian (1920) first described this supernormality in the frog heart.

This historical synopsis must not be closed without reference to the fact that advancement in knowledge of the processes of excitation and conduction in the heart have depended in large measure upon the development of instrumentation Einthoven's (1903) string galvanometer has played a very important role in the study of excitatory processes Most recently the study of individual heart cells by techniques of intracellular recording (Coraboeuf and Weidmann 1949) has made possible a more exact comparison of the responses of cardiac tissue with those of skeletal muscle and nerve These latter tissues have been studied much more extensively and more is known concerning processes involved in their excitation and response Comparable studies of heart cells have just begun In the subsequent chapters of this book other matters of historical significance will be presented as an attempt is made to employ ancient and modern concepts in explaining the phenomena of cardiac behavior

STATEMENT OF PURPOSES AND SCOPE

This brief review of physiological literature indicates that a portion of our knowledge of the properties and functions of living tissue was first derived from studies of the heart. During the last twenty years however physiologists have made more progress in their search for information concerning the fundamental processes of excitation and response by studying nerve and skeletal muscle. One of the major purposes of this monograph is to relate the modern theories concerning the origin of membrane potential and the processes of excitation and response to the study of the cardiac cell and the reactions of the heart. A great deal has been learned of recent years about muscle contraction and its relation to the membrane transmitted excitatory process (Hill 1950 Szent Györgyi 1951 Sandow and Schneyer 1955) Some use of this information will be made in discussing the various phenomena of response

The experimental projects to be described were undertaken with the thought that new instrumentation and newer concepts might aid in the reinvestigation of the phenomena of cardiac function and the interpretation of cardiac abnormalities Such an enterprise has been favored by many other recent developments Even the increased availability of antibiotics has been of help in such studies It is now possible for the physiologist, relatively untrained in the skills of surgery, to implant

electrodes and thermocouple terminals upon the surface of the heart and maintain animals in good health and comfort for many weeks It is thus possible to test the excitability and responses of the heart and determine how they are modified by cold, fever and many other influences without creation of the abnormal conditions attendant upon thoracotomy and exposure of the heart

Cardiac catheterization is now standard procedure and pressure recording devices are available for measurement of pressures and responses in all cardiac chambers and in veins and arteries Other forms of instrumentation have been improved enormously of recent years and the possibility of furthering investigation by means of electronic recorders seems almost inexhaustible This monograph reports methodologies and apparatus developed in the study of some of the basic properties of the heart and its component cellular elements

Recent advances in cardiac surgery and the use of cold to create conditions favorable for such procedures have created new problems The occurrence of cardiac arrest in surgery, the ever present problem of cardiac arrhythmias and fibrillation and a growing general concern over the increasing prevalence of cardiac disease have also suggested that the basic functional properties of the heart should be reinvestigated

It is obvious that a study of excitability and the excitatory process might provide one of the most direct approaches possible to the understanding of the fundamental processes of cardiac function It was decided therefore to reinvestigate the changes in excitability of the heart during the cardiac cycle, to study latency of response, and to endeavor to determine what processes are involved in conduction and the initiation of contraction The effects of certain drugs and various physical agents upon these phenomena were likewise thought to be worthy topics for investigation It was felt that much could be learned about the action of nerves, humoral mediators and hormones upon the heart and its component parts It was decided that in addition to studying the responses of the intact heart the reactions and properties of individual cellular elements of various cardiac tissues would be investigated Much of the information to be reported in this monograph has been derived from these projects

In addition to presenting a report of results obtained and the methods employed in this research enterprise, it is the purpose of this monograph to indicate various lines of new and possibly fruitful study

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II Excitability and the Excitatory Process

A description is given of present concepts of the initiation and propagation of activity in living tissue An attempt is made to relate new information obtained chiefly from studies of nerve and skeletal muscle to the explanation of cardiac excitability

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A STUDY OF THE EXCITABILITY OF THE HEART is aided by knowledge of the processes involved in evoking responses from nerve skeletal muscle and other body components The ability of all tissues to show some reaction to environmental change is known as *irritability* This word implies not only the quality of being responsive but also a sensitivity to or ability to be affected by a stimulus Although the concept of irritability is a very old one the term was not coined until 1672 by Fr Glisson Albrecht v Haller (1753) employed another word *excitable* in describing muscle to indicate that muscle contracts when stimulated It has become customary today to use the term *excitability* more frequently than *irritability* and to describe as excitable only those tissues such as nerves muscles and glands which respond to disturbing forces by a rapid easily detectable reaction.

The development of our knowlege of excitability stimulation and the initiation of response has been traced in many reviews (Biedermann 1895 Verworn 1913 Lillie 1923 Fulton 1930 Katz 1939 Bishop 1941 Hoff 1942 Marchand and Hoff 1955) This chapter therefore will deal rather with those modern concepts which will be of aid in presenting the theories and discussions of this monograph.

THE CELL MEMBRANE

Excitable tissues consist of cells having a characteristic surrounding membrane cytoplasm and cytoplasmic inclusions such as the nucleus mitochondria vacuoles, fibrils etc Some cells possess in addition surrounding sheaths which affect their function. It is known that metabolic processes occurring in the cytoplasm are important to both cell and membrane function. Recent work, however tends to emphasize the fact

that the complex *reactions involved in excitation and transmission of* excitation take place at the cell surface For example, a squid giant axon from which the axoplasm has been displaced by an electrolyte solution will continue to respond to stimuli and to conduct action potentials (Grundfest, et al, 1954) In addition, an electrode can be inserted longitudinally into such a squid axon without modifying the membrane potential but excitability is lost as soon as the electrode scrapes the inner surface of the membrane (Hodgkin and Katz, 1949) Furthermore, the contraction of muscle is intimately linked with membrane responses as are the secretory activities of glands External stimuli must of course affect the membrane first and chains of reactions within both the membrane and other cellular components are touched off by forces acting on the surface structures For this reason more detailed knowledge of the physical and chemical composition and metabolic activity of the membrane is essential

FUNCTIONAL STRUCTURE The membrane is not a simple structure Numerous descriptions have been given of its properties but each tends to emphasize those characteristics detected by the methods used in that particular study Cellular membranes all possess a selective permeability, some substances diffusing through with ease while others are excluded The size and configuration of molecules seem to be of importance in determining their ability to penetrate this observation has given rise to a pore theory of membrane permeability (Hober, et al, 1945) The chemical nature of compounds is important too and certain lipoid soluble materials pass through cell membranes quite readily despite a relatively large molecular size It has been found that the membrane does contain lipid materials in high concentration and lipid containing membranes can be constructed which resemble the plasma or cell membrane in many particulars It is known, however, that some materials which are not lipid soluble penetrate the membrane with ease indicating the presence of other membrane constituents There is ample evidence to show that the membrane also contains a protein component (Davson, 1951, Davson and Danielli, 1952) Thus the cell membrane appears to be a bimolecular or multimolecular sheath 50 to 100 A° in thickness comprised of protein and lipid molecules intimately bonded together and presenting a highly complex surface morphology A schematic representation of this bimolecular lipo protein membrane is seen in Figure 2 A The best available pharmacological evidence also indicates that the cell membrane is not completely homogeneous in composition Some drugs can affect tissue

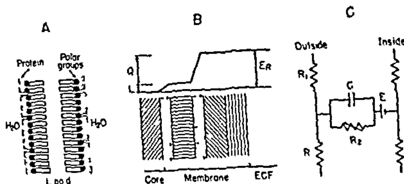


FIGURE 2. Various concepts of cell membrane structure

A. Lipoid protein double layer redrawn from Davson and Danielli 1952.
B Membrane diagram of Lorente de No 1947 ER—Membrane potential Q—Quick fraction L—Labile component ECF—External tissue fluid.
C. Circuit diagram of membrane Longitudinal resistance (R) transverse resistance (R_1) capacity (C) source of potential difference (E)

function in such low concentration that they could not envelop all cell membrane surfaces they are therefore thought to act on specific receptors (acetylcholine on the heart Thienes 1945)

Physiological evidence supports the view that cell membranes should be represented as comprised of at least two concentric double layers Biedermann in 1895 recognized that there were two components in the electrotonic membrane potentials This matter has been studied more fully by Lorente de No (1947 b) who describes a quick (Q) and a labile (L) fraction of the electrotonic potentials which demonstrate differential sensitivity to metabolic alterations (Lloyd 1955) thus suggesting that the membrane has a dual structure To facilitate explanation of these observations Lorente de No postulated a multilayered membrane (Figure 2 B) in which the innermost layer gives rise to the L and the outermost to the Q fraction of the electrotonic potential

Other tests of the properties of membranes permit a still different model to be constructed (Figure 2 C) Descriptions and explanations of the excitatory process are now given almost entirely in terms of resistance charge polarization impedence capacitance etc. which are referred to as electrical properties of the cell membrane The rather exclusive use of this analogy however does not imply that other factors are not involved in membrane reactions Although present knowledge of the metabolic processes underlying excitability and the response to stimulation is still

quite limited, some functional interpretations of this model (Figure 2 C) will be presented in subsequent discussions

EXTRAMEMBRANOUS SHEATHS These structures, which surround some cells, must not be ignored in studies of the chemical and physico chemical reactions which play an important role in maintaining the resting state of the cell as well as in producing the phenomena observed during its activity These sheaths have marked functional significance as indicated by studies of the epineurium of nerves (Lorente de No, 1952, Crescitelli, 1952, Shanes and Berman, 1953) The role of the myelin sheath in conduction (Frankenhaeuser, 1952, Tasaki, 1952) also is well known Although such external structures, when present, are not without effect on cellular activity, excitation and response are primarily dependent on reactions of the cell membrane proper and it is possible to explain most of the observed phenomena solely in terms of known properties of this structure

ELECTRICAL PROPERTIES OF CELL MEMBRANES

The following discussion will adhere to the commonly employed practice of relating the excitability of tissues to known physical and electrical characteristics of the membrane

MEMBRANE POTENTIAL Recording electrodes in contact with the surface of a nerve or muscle reveal no difference of potential between any two points on the tissue provided it is uninjured If, on the other hand the tissue under one electrode has been injured by heat, pressure, concentrated KCl or other means, a potential difference is observed The magnitude of this potential may vary from 10 to 60 millivolts depending upon recording techniques and shunting The injured area is negative with respect to the rest of the tissue i e, current flows in the external (recording) *circuit from the electrode on normal tissue to the electrode* on injured tissue (see Figure 3 B) This injury or demarcation potential (Du Bois Reymond, 1843, 1848-84) is present while the tissue is at rest (Matteucci, 1841) but changes with activity as will be discussed subsequently Observation of this injury potential provided *the first evidence* of the existence of a membrane potential i e, evidence *that the external surfaces of* membranes of excitable tissues are positively charged with respect to their inner surfaces or the interior of the cell

A more direct measurement of this transmembrane potential of resting cells can be made Such measurement permits a better *understanding of*

the injury potential and supports the conclusions already stated The technique employed to record and study transmembrane potential (see also Chapter V) involves use of a glass capillary or microelectrode 0.5 micron in tip diameter and filled with 3 M KCl. Such electrodes can be inserted through the membrane into the axoplasm of a nerve or heart cell without producing either injury or any significant change in the electrical properties of the tissue (Nastuk and Hodgkin 1950 Draper and Weidmann 1951) This microelectrode is paired with a surface electrode and the resting membrane potential directly measured with suitable recorders It is found that a large potential difference exists across the membrane the inside being 60-90 mv negative with respect to the outer surface This so-called resting potential (membrane or transmembrane potential) is of similar sign and magnitude in all excitable tissues studied (Table 1)

TABLE 1—*Resting Membrane Potentials of Excitable Tissues*

Tissue	*R.P.*, mv	*Source*
Squid Giant Axon	61	Hodgkin 1951
Carcinus Axon	82	Hodgkin 1951
Sepia Axon	62	Weidmann 1951
Frog Sartorius Muscle	88	Nastuk and Hodgkin, 1950
Dog Ventricle	85	Hoffman and Suckling 1952a
Dog Auricle	85	Hoffman and Suckling, 1952a
Frog Ventricle	64.5	Woodbury et al., 1951
Rat Ventricle	88	Hoffman and Suckling 1952b
Smooth Muscle Taenia Coli	26-75	Bulbring 1954
False Tendon of Dog Ventricle	90	Draper and Weidmann 1951
Embryonic Chick Ventricle	39.3	Fingl et al., 1952
Cat Auricle	60.4	Burgen and Terroux 1953
Mouse Tibialis Anticus	100	Bennett et al., 1953
Cat Motor Neurone (Spinal Cord)	75-80	Brock et al., 1953

The demarcation (injury) potential is thus seen to result from the transmembrane potential and the effect of injury on membrane resistance (see below) Current is permitted to flow from the normal (positively charged) surface through the injured membrane to the axoplasmic core which is *negatively charged* with respect to the surface. A detailed discussion of injury potential can be found elsewhere (Glasser 1944 p 35 Lorente de No 1947 a and b Lepeschkin 1951) It suffices to state here that, due to shunting the injury potential is much smaller in amplitude than the actual transmembrane potential.

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not behave as a simple cylinder of salt solution but rather as a cable possessing a core of relatively low resistance (the axoplasm) surrounded by a membrane of high resistance which serves to insulate the core from the surrounding fluid. Because of this structure current is channeled along the axoplasmic core and passes out through the membrane only with difficulty however since some current does leave each area of membrane the current density along the core and the potential difference along the membrane decrease with distance from the current source. This concept of the nerve acting as a core conductor was originally advanced by Matteucci (1863) and expressed in more modern form by Hermann (1879) A detailed mathematical treatment of this concept can be found elsewhere (Lorente de No 1947 b) A diagrammatic representation of the axial current flow in nerve is shown in Figure 3 A.

MEMBRANE CAPACITY An additional observation made in studies of the membrane is that after current has been applied the potential difference created requires a certain time to reach a steady value Similarly when the applied current abruptly ceases the local potential previously created by the current decays slowly (Figure 7) This suggests that there are capacitative elements in the membrane which require a finite time to discharge and charge The existence of this membrane capacity is also demonstrated by the observation that if excitable tissue is placed in a bridge circuit, the bridge cannot be balanced without introducing more capacitance into the balancing arm than is required to obtain balance if the electrodes are in a salt solution (Hober et al, 1945 Osterhout and Hill 1930 Cole 1949)

ELECTROTONUS AND ELECTROTONIC POTENTIAL Nerve is known to possess some properties resembling those of a simple resistance capacity network. Since the behavior of tissues even toward very weak polarizing voltages however can seldom be exactly simulated by such a model (Cremer 1929 p 247) Lorente de No (1947) suggests use of the term physical electrotonus to indicate the effects of current flow through such models in order to emphasize their imperfections It can be considered that this physical electrotonus is involved in the establishment of states observed to develop in a nerve when current flows through its membrane.

The passage of current through a nerve causes in association with the state of physical electrotonus changes in the excitability of the fiber In particular there is an increase of excitability at the cathode (catelec-

MEMBRANE RESISTANCE AND THE CORE CONDUCTOR THEORY Membranes offer resistance to both longitudinal and transverse current flow This can be demonstrated when current flows between two electrodes, one of which is adjacent to the inner surface, the other applied to the outer surface of the membrane of a nerve immersed in a large volume of saline In such an experiment the flow of current across the membrane from the external source will, *if the surface electrode is a* cathode, decrease the normal resting potential sustained by the membrane metabolism If the current flow is kept small, however, its physical effect is minimal In the discussion of the next few paragraphs this is assumed to be the case and consideration *is given only to current flow* and the potential differences caused by such current

In this theoretical case recording leads placed at various points along the fiber show that neither the current flow nor the changes in potential produced are confined to the area of membrane lying immediately between the external and internal electrodes On the contrary a potential difference is found between any two points along the nerve until both the recording leads are at considerable distance from the current source Moreover, the potential difference between any two adjacent points on the surface of the fiber is greater than between similarly distant points in the conducting solution surrounding the nerve If current is caused to pass between two surface electrodes there is a similar dispersal of current flow (Figure 3 A) These observations are explained by the fact that the nerve does

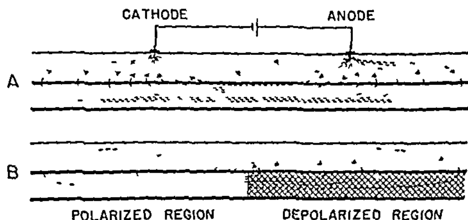


FIGURE 3 A comparison of the curernt flow created by application of the cathode and anode of a battery to nerve (A) and that created in nerve by a depolarized area of membrane (demarcation or injury current) (B)

A stimulus is any environmental change which can induce a reaction Stimuli are termed threshold (adequate liminal) or subthreshold (inadequate subliminal) depending on whether or not they are capable of evoking the characteristic response of the tissue. Tissues have a definite sensitivity to stimuli Thus for a given arrangement of cells, electrodes and sources of electric current, it is found that a current flow of a certain magnitude may evoke the typical response while a current flow of slightly lower magnitude will not. This just sufficient stimulus strength is called the "threshold of the tissue It will be seen more clearly later that it is not possible to obtain an "absolute" threshold when using external elec trodes. The stimulating efficacy of the current depends on how much of it penetrates the fibers and thus in turn will depend in a generally unpredictable way upon the precise properties of the electrodes and the distribution of current within the tissue Nevertheless for a given experiment, with electrode properties location and the time-course of current held constant, the threshold will be a well defined and reproducible quantity

STRENGTH DURATION REQUIREMENT The threshold of a tissue even to electrical stimulation is constant only for a current pulse of fixed shape and duration Thus when employing rectangular current pulses, weaker strengths will timulate if allowed to flow for longer times. Hence, given a fixed pair of electrodes in a definite location one can obtain a curve of threshold as a function of duration of the stimulus. This so-called strength duration curve shows that as duration of current becomes longer and longer the threshold falls but does so more and more slowly until a minimal level is reached A lesser intensity of current does not stimulate no matter how long it is allowed to flow The minimal level which will stimulate if allowed to flow for a sufficiently long time is called the *rheobase* and the time during which the rheobasic current must flow in order to stimulate is called the *utilization time* It is evident that brief stimuli must be of high intensity to be effective and if too brief in duration timuli do not excite at voltages normally employed in biological research The strength duration requirements for tissue stimulation have been very thoroughly studied (Hoorweg 1892 Weiss 1901 Fredericq 1928) Figure 4-A and B shows strength-duration curves typical of cardiac muscle both auricle and ventricle These curves are similar though the rheobasic requirements were not identical

It is somewhat laborious to obtain the entire strength-duration curve

trotonus) and a decrease of excitability at the anode (anelectrotonus) These changes in excitability, observed by Ritter (1802 1805) and studied intensively by Pfluger (1859) are known as physiological electrotonus and will be discussed later in conjunction with the local excitatory state

Recording electrodes placed on the membrane, one near and one far from the region of current flow, show a potential difference Near the cathode there is a decrease and near the anode an increase in membrane potential As stated previously some time is required for these electro tonic potentials to reach their peak after current flow begins and some time to decay after applied flow ceases Such localized potentials also are created by other subthreshold stimuli and locally acting excitatory processes

In summary, the passive electrical properties of the nerve can be described as follows the membrane possesses a relatively high resistance and capacitance and insulates the axoplasmic core from the extracellular fluid Potential differences applied across the membrane give rise to current flow which finds a preferential longitudinal pathway via the axoplasm and extracellular fluid since these have a lower resistance than has the membrane In addition there is a large potential difference, of the order of 0 1 volts, across the resting membrane with the inside of the cell negative to the external surface Thus the nerve can be represented by a simple electrical circuit containing a battery, a condenser and variable resistances (Figure 2 C)

THE STIMULUS

The excitability of a tissue is judged in terms of the work required to affect it This work performance or stimulus can be of several types and the sensitivities of various tissues to specific forms of energy vary markedly Locally applied heat or cold, pressure, osmotic force, various chemicals, light and sound, all affect at least some cells of the body It is well known that some types of stimuli excite practically all cells but other stimuli excite only specialized receptors The type of stimulus most commonly employed to estimate the excitability of a tissue is electrical current Not only can the quantity and duration of applied current be controlled and measured easily but also its effects on tissues are readily reversible and no injury is caused by currents much stronger than those required to stimulate As a matter of fact, normal excitatory processes evoke a transfer of charge and thus a current flow similar to that applied in electrical stimulation

characteristic of a tissue in determining its excitability It is also not completely satisfactory to describe excitability merely in terms of the rheobase since this expresses only one part of a stimulation requirement. Lapicque (1926) endeavored to describe the excitability of a tissue in terms of two values (1) the *rheobase* and (2) *chronaxie* which is defined as the minimum time required by a current of twice rheobasic strength to effect stimulation This arbitrary method has its usefulness but should be regarded merely as a convenient substitute for the complete determination of stimulus strength and durational requirements (Davis and Forbes 1936) It can be seen from Figure 4-C, depicting strength duration curves of cardiac muscle how misleading a criterion of excitability chronaxie may be The methods used for quantitatively determining excitability must be chosen with proper regard for the requirements of the situation

OTHER REQUIREMENTS In studying the excitatory process by determining the effects and requirements of electrical current flow it is found that when a stimulating current commences the preferential site of origin for the propagated response is the cathodal surround (Katz 1939 Orias et al 1950) It is also generally stated that restimulation does not normally occur repetitively during a period of unaltered current flow There are exceptions to this statement which will be discussed later Ordinarily the make of a direct current is more effective than the break, stimulation occurs at the cathodal region on the make and near the anode on the break very rapidly alternating currents do not excite. Another determinant of the efficacy of a stimulus is its shape—that is the rate of change of the current flow A stimulating current which suddenly changes from zero to full strength (a rectangular pulse) is more effective than one which rises slowly A current strength which is of threshold value when applied suddenly will fail to stimulate if the rate of rise to this strength is somewhat slower If current strength rises sufficiently slowly stimulation will not occur at even very high intensities The ineffectiveness of slowly rising current strengths is the result of a change in threshold called *accommodation* This phenomenon will be discussed in greater detail later

FIGURE 4. Strength-duration curves expressing excitability of the auricle (A) and ventricle (B) of a dog heart. C is a family of strength-duration curves each taken at a different time following the beginning of electrical activity in heart muscle (beginning of a cycle) showing that chronaxie does not give an ad quate indication of the state of excitability during recovery

A

AURICLE

STRENGTH OF STIMULUS IN MA

DURATION OF STIMULUS IN MSEC

B

VENTRICLE

STRENGTH OF STIMULUS IN MA

DURATION OF STIMULUS IN MSEC

C

1 -- INTERVAL 450
2 -- 230
3 -- 200
4 -- 160
C -- CHRONAXIE
R -- RHEOBASE

STRENGTH OF STIMULUS IN MA

DURATION OF STIMULUS IN MSEC

FIGURE 4 *(See legend facing page)*

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THE EXCITATORY PROCESS

It is probable that the intrinsic excitatory process which initiates contractions of smooth and cardiac muscle and the spontaneous origin of impulses in nerve cells act in the same way as do applied stimuli, and it is apparent that both types of stimulation will initiate a normally propagated response Knowledge of initiation of activity in sense organs and in the pacemakers of spontaneously active tissues can be gained from a study of the mechanism of excitation by applied electrical stimuli

The mechanism of action of stimulating influences has been discussed rather thoroughly in the past (Nernst, 1908, Hill, 1932, Blair and Erlanger, 1936, E A Blair, 1938, H A Blair, 1938, 1939, Katz, 1939) Recent work has contributed much to our knowledge of what happens in the membrane when effective electrical stimuli are applied Localized changes in the membrane are first produced and if these are of sufficient magnitude they give rise to propagated effects A consideration of the phenomena associated with excitation will serve as introduction to an explanation of their origin

THE LOCAL EXCITATORY STATE Current flow creates in the region of the cathode a local excitatory state This term, local excitatory state (Lucas's "local disturbance") as commonly employed in discussions of excitation and response is without definite implication as to what the processes involved in creating this state may be Any stimulus produces a local excitatory state preliminary to actual stimulation Subliminal stimuli create local excitatory states in cell membranes An excitatory state is created adjacent to the borders of a depolarized or injured area by current flow engendered from the sink source relationship Use of the term does imply that the basic disturbance involved is not propagated, that the condition has a definite but short temporal duration and that no irreversible changes have taken place The processes involved in the production of a local excitatory state are not of an all or none character

The existence of a local excitatory state can be demonstrated by use of testing stimuli of subthreshold intensity or by recording the local response associated with this state Discussion of these two procedures follows

SUMMATION OF INADEQUATE STIMULI When a stimulus too small to evoke the characteristic response of the tissue is followed quite soon by another stimulus of equal or even smaller magnitude, a response may be evoked Furthermore, if two stimuli, each too small to excite,

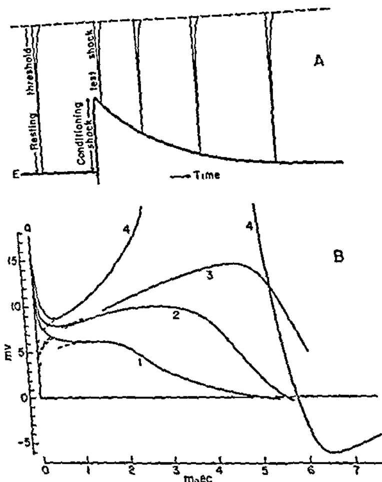


FIGURE 5. Evidence of the existence of a local excitatory state

A. Change in excitability (E) resulting from a subthreshold conditioning shock. The presence and time course of the excitatory effect is determined by the strength of test shocks required to stimulate (latent additional stimuli) (Redrawn from Katz, 1939.)

B. Local response produced by subliminal stimuli of increasing strength in a non medulated nerve fiber (1 2 3) and the beginning and end of a propagated response (4) initiated by a stimulus of threshold strength. a—stimulus artefact. Dotted lines show approximate time course of local responses. (Redrawn from Hodgkin and Huxley 1952 a.)

are applied simultaneously to nearby points of the same fiber, excitation may occur These two types of addition of stimulus effects are known respectively as temporal and spatial summation Temporal summation occurs when stimuli applied later in time than the conditioning stimulus superimpose their effects in the same membrane area Spatial summation implies supportive action between stimuli applied to adjacent areas This use of the term spatial summation differs somewhat from that employed in discussion of reflex action in which the term is employed to indicate that stimuli applied to different sensory endings summate their effects if the afferent fibers from these stimulated endings converge upon the same central neurone pools

Temporal summation depends on the capacitative properties of the membrane, i e , the ability to accumulate and retain the effects of current flow Spatial summation in the membrane depends rather on the resistive properties which cause some diffuseness of effect rather than a localization of current penetration of the membrane merely at the point of *electrode* application

The phenomenon of temporal summation permits determination of the magnitude and duration of the effects of subthreshold stimuli, i e the intensity and duration of a local excitatory state Figure 5 A gives in diagrammatic form the procedure followed in testing the effects of a local excitatory state or response The amplitude of the test shock required to produce a propagated response gives indication of the rise and decline

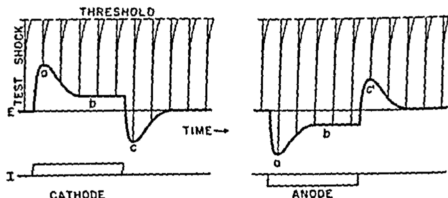


Figure 6 A diagram of catelectrotonus and anelectrotonus in nerve E—Excitability changes under the cathode and anode during and following a subthreshold stimulus of long duration I—Time of current flow Initial enhancement (a) and depression (a) of excitability The effect of accommodation (b and b) Post cathodal depression (c) and post anodal enhancement (c)

of effects caused by the initial stimulation The local effect at the anode is approximately the reverse of that occurring at the cathode.

When current flow is of long duration, the excitability changes at the cathode and anode are more complex. Initially, as shown in Figure 6, there is a build up of a local excitatory state in the region of the cathode and a local depression under the anode Adaptive processes or counter actions soon come into operation to reduce the effectiveness of the current and this is called accommodation (Erlanger and Gasser, 1937 Katz, 1939) At the break of a long continued current flow conditions under the two electrodes reverse There is a depression of excitability under the former cathode and an increase in excitability at the site of the original anode The extent of the initial changes and this reversal depend upon the density and the duration of the current flow employed

A theoretical explanation of these phenomena will be offered later after a consideration of the mechanisms underlying *excitation* It suffices to say here that the use of testing stimuli and summation has permitted determination of these effects of subliminal and long continued current flow on tissue excitability The changes in membrane potential associated with these changes in local excitability have been considered to constitute a local response

SUBTHRESHOLD ACTIVITY (THE LOCAL RESPONSE) Records obtained by means of an intracellular electrode paired with a surface electrode show that when a weak subthreshold stimulus is applied to a nerve the transmembrane potential under the cathode is displaced toward zero during and for a period after the current flow The time course of the displacement depends upon duration of the stimulus and the value of the membrane capacity If however the stimulating current is progressively increased by equal increments it can be seen that the further displacements of the membrane potential are not proportional, progressively larger depolarizations result from each step in stimulus strength (Figure 5) This behavior of the membrane potential in response to subliminal stimuli is called subthreshold activity or a 'local response" and consists of graded activity on the part of a small area of membrane (Katz, 1937 Hodgkin, 1939 Marmont, 1949 Cole 1949 and Rosenblueth 1952) In other words the displacement of membrane potential during a local response is not purely passive but is contributed to by a change in properties and processes going on in the membrane itself

Surface recording electrodes can likewise detect evidence of this local

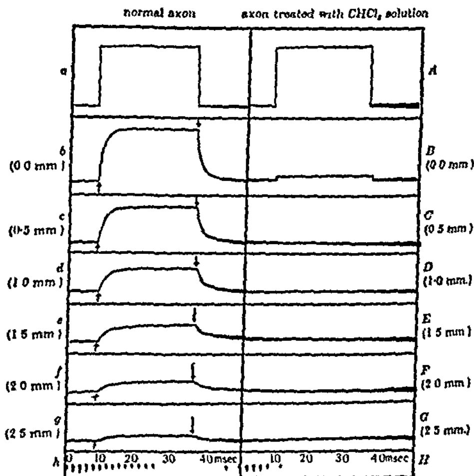


Figure 7 Electrotonic potentials in nerve *Series on left shows spacial decrement of electronic potential as recorded from the surface of the muscle at points progressively farther from point of subthreshold stimulation (b g) Series on right shows change in electrotonic potentials following treatment of membrane by chloroform (B G) (From Hodgkin and Rushton Proc Roy Soc B 1946) a and A show the shape of polarizing pulses Time in msec and distance in mm indicated*

response or subliminal change *in membrane state* when one lead is adjacent to the *stimulating* cathode A non propagated *negative potential* develops which is augmented progressively by increases in applied current If the local potential recorded either by surface or *intracellular* leads attains a critical amplitude it gives rise to a propagated spike or action potential (Figure 5 B and 7)

That these local or subthreshold responses are related to the local

excitatory state discussed previously can be demonstrated by applying test shocks during intervals corresponding to various phases of the recorded local response. The strengths of the latent additional stimuli required to produce a propagated response at various instants after the conditioning shock are inversely related to the amplitude of the local response The strength required increases progressively as the local potential decays

THE ACTION POTENTIAL When stimuli at or above threshold strength are used there rises from the small potential associated with the local response a spike like action potential which is propagated along the fiber stimulated The transmembrane action potential typical of nerve is preceded by a relatively minute prepotential or local response, has a rising phase a period of overshoot indicative of a reversal of membrane polarity a falling phase and in certain cases a positive after potential.

The action potential is the electrical sign of changes created by the excitatory process taking place in the membrane Du Bois Reymond described the action potential (1842) and both Engelmann et al. (1873) and Eyster et al (1938) actually recognized the occurrence of the overshoot or reversal phase of the action potential of the heart. However since surface recording involves some uncertainties the accurate delineation of the magnitude and time course of the action potentials of various tissues was not possible until the advent of transmembrane recording (Hodgkin and Huxley 1939 Curtis and Cole 1942) This typical response of an excitable membrane the action potential is thus best recorded by means of an intracellular electrode paired with another electrode on the surface of the membrane When this technique is employed the response to a threshold stimulus is as shown in Figure 8 Following application of the stimulus the resting membrane potential does not disappear as would occur in case of mere depolarization but continues to change at a very rapid rate until the transmembrane potential in the region of the applied stimulus actually reverses its polarity the inside of the fiber becoming positive with respect to the outer surface The rising phase of the spike or action potential may overshoot the zero level by 20-50 millivolts Following attainment of the peak of reversal the transmembrane potential begins its return to the resting value at a rate somewhat slower than that of the rising phase Thus the rising or "depolarization" phase of the action potential terminates in a falling or "repolarization" phase which varies greatly in time course as will be seen subsequently

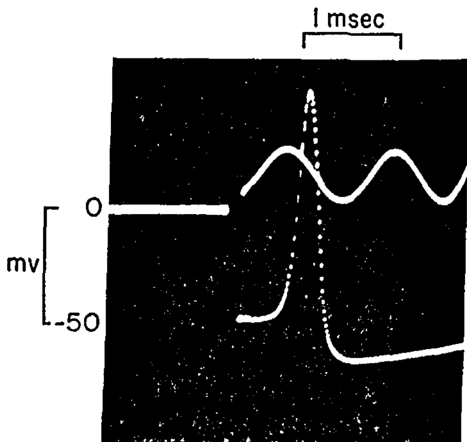


FIGURE 8 Action potential of squid giant axon recorded at 20 C by means of an intracellular microelectrode Straight line zero potential Sine wave frequency 1000 c p s (Unpublished photo C. Y Kao) Voltage calibration as indicated

The general magnitude of the action potential is similar in all excitable tissues that have been studied However, it can be seen from Figure 9 that action potentials obtained from different types of cells possess certain dissimilarities In addition to differences in duration there appear to be differences in components Negative and positive after potentials are seen in nerve and skeletal muscle as well as an initial spike and overshoot Heart muscle cell potentials show a plateau phase not seen in action potentials recorded from nerve and skeletal muscle but there are no obvious negative and positive after potentials Furthermore, all cardiac cellular potentials are not identical A potential of short duration with little or no plateau is obtained from auricular cells but long lasting potentials with

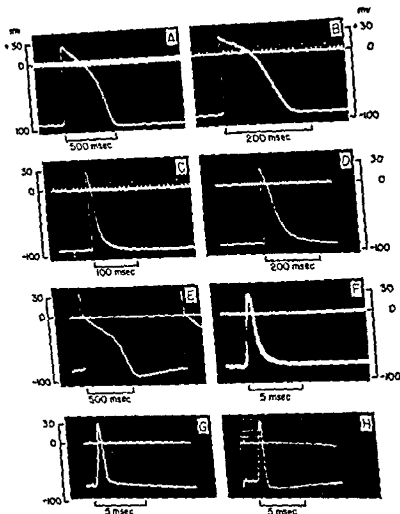


FIGURE 9 Transmembrane potentials of various excitable tissues. A—Frog ventricle B—Dog ventricle C—Rat ventricle D—Dog auricle E—Kid Purkinje fiber, F—Rat diaphragm G—Squid axon H—Sepia axon Voltage calibration A through G +30 and −100 mv In H calibration lines of 10 mv O—zero potential. Time calibrations A—500 msec. B—200 msec. C—100 msec. D—200 msec. E—500 msec. F H—5 msec. (Retouched to show action potential upstrokes by dotted lines.)

a clearly differentiated plateau are obtained from cells such as those of the dog ventricle Potentials from single fibers of the Purkinje system and other specialized tissues taken when these cells are serving as pacemakers are still different in that they show a marked prepotential Much more will be said concerning these cardiac cellular potentials and their functional significance in Chapter V

THE PROPAGATED ACTION POTENTIAL—SURFACE RECORDING Intracellular recording is best for analysis of the action potential but *methods of surface recording are more readily employed in studies* of propagation of excitation and the conduction of the action potential

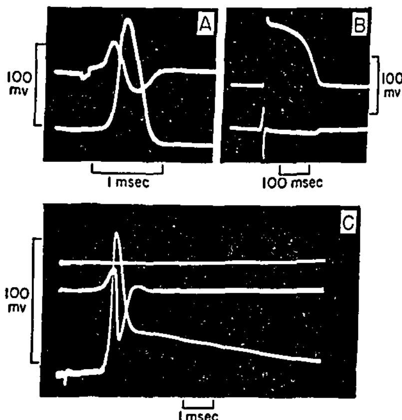


FIGURE 10 Comparison of surface and transmembrane potentials
A. Squid nerve (upper tracing—bipolar surface recording)
B Dog ventricle (lower tracing—unipolar surface recording)
C Frog sartorius (upper tracing—line of zero potential middle tracing—unipolar surface recording)

along nerve fibers and in the myocardium In all forms of recording the deflections obtained merely indicate an imbalance between paired elec trodes as the wave of activity the propagated action potential, passes beneath or through the area specifically surveyed by these electrodes. When electrodes applied to the surface of the tissue are used to pick up nerve or muscle potentials the activity in a number of elements nerve fibers and muscle cells is recorded The shapes sizes and durations of such action potentials therefore are determined by the synchronization of the activity occurring as well as by the configuration and duration of the action potentials of the individual cells involved

Figure 10 shows various types of action potentials recorded in such routine studies of nerve skeletal muscle and the heart. The types of cellular potentials as obtained by use of an intracellular electrode which summate to produce these directly and indirectly recorded action poten tials are also shown It is obvious that the components of these surface recorded or compound potentials must arise in part from a temporal dispersal of activity in the cell population The derivation of compound potentials such as the electrocardiogram from an association of cellular action potentials will be discussed in Chapter V

The changes in membrane properties and the processes initiated in cells by an effective stimulus which give rise to the action potential will be discussed in considerable detail after a brief consideration of the phenomena of conduction and the refractoriness which develops following excitation and a response

CONDUCTION—THE PROPAGATION OF A RESPONSE

Conduction or the process by which excitation travels from its point of origin to other parts of a tissue involves a sequential depolarization of each contiguous segment of the irritable structure In recent discussions of conduction there have been two emphases as though there were either an electrical mechanism *or a chemical* mechanism operating in the production of this phenomenon As a matter of fact, electrical chemical and physical processes participate as can be demonstrated in numerous ways The occurrence of chemical processes is indicated by increased metabolic activity and by the action of chemicals such as enzymatic blocking agents The presence of associated physical processes is indicated by observations of, among other things changes in light scattering viscosity and "stick iness" of protoplasm in the active segments of conducting tissues (D K.

Hill, 1950 a and b, Tobias, 1952) For the present, however, discussion will be confined to the electrical events giving rise to conduction of excitation

The present view most generally accepted is that conduction originates from a local circuit built up at the point of stimulation and a consequential current flow spreading out in advance of depolarized segments of the membrane This local circuit concept follows directly from the core conductor theory of Hermann (1879) and can be explained as follows As soon as an area of *membrane under a stimulating electrode is depolarized* (depolarization plus reversal initiated), there is created a sink source contiguity in a conducting medium and this can only result in a local current flow (Figure 3 B) The direction of this current, by standard convention, is from the positively charged or inactive areas into the area which is active and thus is electrically negative In explaining the consequences of this local current flow it can be said that the current is such that the resting membrane is depolarized Although the currents spread out along the cellular elements and through the surrounding conductors, they are of highest intensity close to the active region or sink and serve to stimulate the adjacent segments of membrane much as does the cathodal current under a stimulating electrode Conduction, therefore, is *due to* intrinsically created current flow which travels over the tissue depolarizing or stimulating in new areas as the previous or upstream sinks are repolarized by virtue of intrinsic processes of recovery

THE STIMULATING EFFICACY OF THE ACTION POTENTIAL Perhaps the greatest difficulty in accepting the concept that the eddy currents, engendered by proximity of active and inactive membrane areas, invade and stimulate resting tissue arises from a comparison of the possible strength or amperage of such local current flow with the threshold requirements of artificial stimulation This difference is largely explained by the shunting which occurs in artificial stimulation with electrodes placed on the surfaces of tissue Stimulation by means of an intracellular electrode paired with one on the surface of a cell requires the passage of only microamperes of current Furthermore, there is ample evidence of the stimulating efficacy of current flow created by localized membrane depolarization For instance, Wedensky facilitation (Hodgkin, 1937 b) *provides an example of* excitatory influence acting across small segments of injured or blocked membrane The electrotonic or eddy current flow engendered by an action potential approaching a block partially depolar

izes the membrane distal to the block. The extent of this depolarizing or excitatory action can be estimated by the use of sub-threshold testing stimuli It is thus found that these eddy currents produce a localized excitatory state comparable to that resulting from a conditioning subthreshold stimulus The highest concentration of eddy current naturally falls within the blocked area and it is reasonable to suppose that had this been excitable membrane the eddy current would have constituted an effective stimulus Calculations based on experiments of this type have lead to the conclusion that the stimulating power of the action potential is three (Bishop 1951) to ten (Hodgkin 1937 a) times that which is required to excite the normal nerve membrane

This evidence that eddy currents can have effects on tissue beyond a block suggests that activity in one group of cells might have effects on adjacent tissues contiguous to but not anatomically connected with the membrane in which activity is occurring This does occur, and the rheoscopic preparation of Matteucci (1842) the observation by Koelliker and Mueller (1856) that the beating heart may stimulate a nerve laid upon it and the evidence of nerve fiber interaction described by Katz and Schmitt (1940) provide support for this conclusion

This concept of conduction indicates that an impulse can move in any or all directions from a stimulated or depolarized area provided continuous membrane surfaces exist. It is true that impulses can be initiated in any part of the heart and will spread to all other regions of the syncytium. Even in the heart there are preferential routes of travel, however, and activity tends to remain confined to fiber pathways Because of the core conduction property of cells activity spreads more rapidly and with less opposition along the longitudinal axes of fibers than it does transversely across fiber pathways In the A V node of the heart (Wiggers, 1949) and at the axon hillock of the motoneurone (Eccles, 1953) one way conduction is favored

Illustrations of the passage of an impulse along a nerve or other fiber might cause one to wonder why the eddy currents following the wave of excitation do not cause impulses to journey back up the fiber before the propagated wave of depolarization reaches and dies out at the nerve terminals The question of normal one way conduction of multiple firing induced by a single stimulus and the reentry of an impulse into previously depolarized but recovering tissue is important. The circumstance normally preventing such occurrences is in brief, the fact that

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an effect which will ultimately produce a propagated response but the latency is greatly prolonged since propagation at normal velocities cannot begin within this irresponsive period It appears that a second propagated response cannot occur until a period of time has elapsed following previously initiated activity The irresponsive period is practically identical in duration with the period of subnormal excitability (the total refractory period) Repolarization of the membrane is essential to restoration of normal excitability and power of normal conduction.

It has become common practice as mentioned above (Carlson, 1906, 1907) to subdivide this interval of subnormality or the total refractory period into an absolute and relative refractory period. This will be discussed in detail later but in preliminary review it can be said that while the boundaries of the total period of subnormal excitability are readily definable statements concerning the duration of the absolute refractory period must be made in terms of the strength and duration of the test shocks employed Recovery from refractoriness is a progressive process and it is difficult to identify an exact moment when recovery *has* progressed far enough to permit a second stimulus to produce an effect which will persist until a propagated response *can* be *initiated* Explanations of the processes going on during the refractory periods *requires some* knowledge of the excitatory processes which reduced the membrane and cell to a state of subnormal excitability and irresponsiveness

PROPOSED EXPLANATIONS OF ELECTRICAL ACTIVITY

Numerous attempts have been made to explain the phenomena related to excitation of living tissue in terms of physical and chemical factors responsible for their appearance This is possible only to a limited extent because of the inadequacies of present knowledge However the theoretical explanations currently *proposed do* give considerable insight into both the behavior of excitable membranes and the possible causes of many of the observed phenomena of excitation.

THE IONIC HYPOTHESIS The ionic theory of excitation (Hodgkin, Huxley and Katz 1952) will be discussed in some detail because the major part of the available *experimental* data can be explained by it quite adequately and because of its general applicability to nerve skeletal and cardiac muscle

Resting potential. It has been known for many years that there is a potential difference of 60-70 *mv* across the membrane of resting nerve

tissue becomes refractory following excitation and thus is not as subject to stimulation by the small following eddy currents as is tissue not previously invaded by the excitatory process There thus are barriers of refractoriness which confine the excitatory process to a one way transmission in fibers initially stimulated

LATENCY OF RESPONSE There is a latency between stimulus and response in any tissue The duration of latency can be determined by measuring the lapse of time between the stimulus artefact (a recorded signal of the applied current flow) and the beginning of the action potential This latency is comprised of (1) the time required for the local response to attain sufficient intensity to initiate a propagated response, and (2) conduction time (the time required for the action potential to travel from its site of origin to the recording electrodes) If one is recording mechanical responses of muscle there is also a latency of contraction to consider In most recording the major latency is due to conduction time It is well known that speed of conduction varies with fiber size (Erlanger and Gasser, 1937) but these matters do not require consideration at this time

REFRACTORINESS AND THE IRRESPONSIVE PERIOD

Muscle and nerve tissues become temporarily inexcitable immediately after the initiation of a propagated response, regardless of the stimulus intensity employed Therefore, refractoriness is a consequence of the response to the excitatory *process* The *period* of refractoriness can be subdivided into an initial phase of absolute refractoriness and a subsequent phase of relative refractoriness during which suprathreshold strengths of stimulation are required to elicit an action potential The post excitation refractoriness has a very short duration in nerve and skeletal muscle (Adrian, 1921) corresponding approximately to that of the action potential In cardiac muscle refractoriness lasts much longer but also has a length comparable to the action potential of an individual fiber When recording the action potential of the heart as a whole the refractory period of the excitability cycle corresponds to the duration of the summed electrical phenomena

Keith Lucas (1909 a and b) observed that a propagated response could not occur immediately after excitation of skeletal muscle and nerve He described this as an *irresponsive* period A similar irresponsive period exists in cardiac muscle Stimuli applied during this period may have

The problem is thus resolved into a question of how the concentration gradients originate and how the observed potential difference the resting potential is produced A full explanation involves considerations of electrochemistry which are beyond the scope of this work but some understanding of the situation may be gained from the following simplified presentation

Let it be assumed as a first proposition that the concentration gradients of ions arise as the result of a metabolic activity of the membrane (activity of the 'sodium pump") which transports sodium out of the fiber and potassium in (Hodgkin and Keynes 1955-a and b) As the concentration of K^+ within the fiber rises, there is an increasing tendency for outward diffusion of positively charged potassium ions. This tendency toward a net loss of positively charged particles from the inside of the membrane creates a potential difference across the membrane so that the inside becomes negative and the outside positive At any instant the magnitude of the potential difference thus created is just adequate to prevent any net diffusion of K across the membrane Thus in spite of concentration differences the K can be said to be in electrochemical equilibrium The tendency to diffuse *from a* region of high concentration to one of low concentration *is prevented* by the membrane potential

A somewhat similar explanation is the following Let it be considered that a fiber permeable to K and Cl but almost impermeable to Na^+ contains the high concentration of potassium and low concentration of sodium and chloride previously mentioned The usually observed potential difference of 70 mv—inside negative to outside also exists If the membrane potential is suddenly lowered *to zero* positively charged K will tend to diffuse out and negatively charged Cl to diffuse in this in turn will restore the original potential difference and net diffusion of either species of ion will cease the concentration gradients being returned to electrochemical equilibrium by the potential difference created

It is evident, *therefore* that the resting membrane potential arises *from* the partition of *ions from* the tendency of these ions to diffuse down their concentration gradients and from the selective permeability of the membrane It is thought that potassium is most directly concerned with the creation of the resting potential because of the relative ease with which K crosses the resting membrane as compared to Na^+ A considerable amount of evidence in favor of this hypothesis has been accumulated In the first place if the membrane were exclusively permeable to K, the

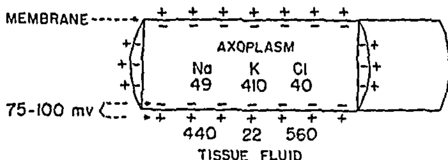


FIGURE 11 Intracellular and extracellular distribution of ions in squid giant axon (Redrawn from Eccles 1953)

and that the interior of the axon is negative with respect to the surface It is also known that the concentrations of electrolytes inside the fiber are quite different from those of the extracellular fluid Figure 11 gives the intracellular and extracellular distribution of ions in the giant axon of the squid, the cell used most commonly in studies of ionic partition and ionic flux These concentrations differ somewhat from those found in mammalian cells but in these latter species also the axoplasm and myoplasm contain much more of K^+ and much less Na^+ and Cl^- than is found in the extracellular fluids (Fenn and Cobb, 1934, Fenn et al, 1934 a and b, Boyle and Conway, 1941, Steinbach and Spiegelman, 1943, Keynes and Lewis, 1951 a and b) Although the absolute values vary considerably in different tissues the approximate ratio is

$$\frac{[K]_i}{[K]_o} = \frac{[CL]_o}{[CL]_i} = 50 \quad \text{and} \quad \frac{[Na]_o}{[Na]_i} = 8 \text{ to } 12$$

Since the resting cell membrane is reasonably permeable to potassium and chloride, although sparingly permeable to sodium (Boyle and Conway, 1941, Conway and Moore, 1945, Shanes, 1946) one would perhaps expect the K^+ and Cl^- to diffuse across the membrane until the concentrations on each side were equal However, since there is a potential difference across the membrane of such a nature that the axoplasm is negative with respect to the extracellular fluid, the tendency of charged ions to redistribute themselves in such a manner as to equalize the existing concentration gradients is opposed by the influence of the negative charge within the fiber, K^+ being maintained within and Cl^- outside the membrane

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potential difference resulting from the potassium concentration gradient could be calculated from the following expression

$$E = \frac{RT}{F} \log_e \frac{[K]_i}{[K]_o}$$

where $[K]_i$ and $[K]_o$ are the activities of potassium inside and outside the membrane and are proportional to the concentrations in each location, and E is the potential difference When the actual values for potassium concentration are substituted in the equation, the calculated membrane potential closely approximates the value directly determined by transmembrane recording (Hodgkin, 1951) Furthermore, it has been known for many years (Hober, 1905, Bernstein, 1912, Hill, 1932) that potassium depolarizes excitable tissue It has also been demonstrated in nerve (Curtis and Cole, 1942, Shanes and Hopkins 1948, Feng and Liu, 1949 a and b Huxley and Stämpfli, 1951 a and b), in skeletal muscle (Ling and Gerard, 1949, Nastuk and Hodgkin, 1950) and cardiac muscle (Burgen and Terroux, 1953) that the resting membrane potential varies, within a reasonable range, as a linear function of the log of the extracellular potassium concentration On the other hand, as would be expected from the above discussion, the magnitude of the resting potential of the same tissues is relatively unchanged by large variations in the extracellular concentration of Na^+ (Hodgkin and Katz, 1949, Nastuk and Hodgkin, 1950, Huxley and Stampfli, 1951 b) Other experimental evidence in favor of the role of K^+ in determining the resting membrane potential is cited elsewhere

The sodium pump Perhaps the most striking aspect of the ionic distributions is the extremely low concentration of Na^+ within the fiber In spite of a high concentration gradient and a resting potential both of which would tend to drive Na^+ inward across the membrane this ion is largely maintained outside the cell It has been stated that the membrane is only slightly permeable to sodium but even with minimal permeability the diffusion of Na^+ would equalize concentration differences unless some additional process were operative Such a process does exist and has been called activity of a 'sodium pump" This term implies nothing concerning the nature of the pumping process but merely suggests that there is an active metabolic extrusion of sodium by the fiber membrane which maintains the observed concentration gradient (Hodgkin and Keynes, 1955 a and b) and permits the membrane potential to be established and maintained

It has been demonstrated that the ion partition and membrane potential cannot persist indefinitely in the absence of metabolic activity (Gerard 1930 1932 Cowan 1934 Lorente de No 1947 Shanes and Hopkins 1948) In addition it is likely that the sodium is transported in a bound form and that there is a simultaneous exchange of K and Na , each sodium ion leaving the axoplasm being exchanged for a potassium ion from the extracellular fluid A well known example of this type of active transport is seen in the exchanges of K Na and H by the renal tubules (Smith, 1951) Because of this exchange there is no net transfer of charge and the metabolic extrusion of Na therefore requires little energy expenditure.

There are several additional aspects of the metabolic extrusion of sodium which are of interest and which will be discussed subsequently in conjunction with a consideration of the production of the *action potential*

The depolarization phase or upswing of the action potential is thought to be due to a sudden influx of Na into the cell resulting from a change in membrane permeability The experiments of Cole and Curtis (1939) and Cole and Hodgkin (1939) demonstrated that the upstroke of the action potential is associated with a marked drop in membrane impedance The specificity of the increase in permeability to Na was subsequently verified by the voltage-clamp experiments of Hodgkin Huxley and Katz (1952) A discussion of this technique may be found in Hodgkin and Huxley s papers of 1952 a and b There can be no doubt that, on excitation membrane impermeability to Na is reduced and the ion rapidly crosses this former barrier under the driving force of both the concentration and potential gradient. Since the permeability of the membrane to K^+ and Cl is at this time very low relative to the Na^+ permeability (Hodgkin and Huxley 1952 a) the contribution of these latter ions is negligible and the membrane potential approaches that a sodium diffusion potential

$\left(E = \frac{RT}{F} \log_e \frac{[Na]_i}{[Na]}\right)$ and since the net membrane current is positive and inward the inside of the fiber rapidly becomes positive with respect to the outside. Thus the rising phase and overshoot (reversal phase) of the action potential are explained by an influx of the positively charged sodium ions The fact that the magnitude of reversal of membrane polarity is somewhat less than that calculated is due to the

onset of inactivation or a reduction in Na^+ permeability and a pronounced rise in K^+ permeability

The repolarization phase or downstroke of the action potential occurs in the following manner Immediately after the upstroke of the action potential a repolarization begins which ultimately restores the trans membrane potential to a normal resting level This repolarization is brought about by means of two processes (1) an outward flux of potassium (Hodgkin and Huxley, 1952 a) and (2) a decrease in sodium permeability Inactivation of a sodium carrier is frequently mentioned in this connection but for the present purposes it suffices to state that there is a reduction of sodium entry into the cell The outward movement of potassium occurs as a consequence of the loss of membrane potential and an increased permeability of the membrane to K^+ The result of these various changes in conditions is that the inward Na^+ current decreases, the outward K^+ current rises, and the net membrane current carried by positive ions is once again in the outward direction This restores the membrane potential practically to the resting level where potential difference just balances concentration gradient and no net ionic flux occurs However, as a result of the action potential the fiber has gained a minute quantity of Na^+ from sodium entry at a rate of 3 $\mu\mu M/cm^2$/impulse and lost an equal amount of K^+ (Hodgkin and Keynes, 1955 a and b) These small changes in ionic distribution are reversed, during the resting state, by the active metabolic extrusion of sodium mentioned previously

Excitation The events leading to production of an action potential are initiated by stimuli Stimulation normally occurs during the flow of cathodal current, that is, current passing *outward* through the membrane and *decreasing* the level of the membrane potential This decrease in membrane potential is associated with an increase in sodium permeability That this is indeed the case has been clearly revealed by voltage clamp studies (Hodgkin and Huxley, 1952 a and b) which demonstrate that sodium permeability is a function of the actual magnitude of membrane potential

The occurrence of excitation can thus be described as follows The stimulus lowers the membrane potential in the cathodal surround, this causes an increase in sodium permeability and a resulting inward current of Na^+ The process thus becomes regenerative or self sustaining and depolarization and the reversal of the membrane polarity result The

threshold for excitation can be defined as a level of membrane potential at which the tendency to regenerative depolarization, due to the factors just mentioned is greater than the tendency toward repolarization

Propagation of an action potential is now easily understood. Current flow from an adjacent, unexcited region into the area initially depolarized lowers the membrane potential of this adjacent region to the critical level. The level of potential at which conditions in the membrane lose their stability is sometimes called the *threshold potential*. When this critical level is increased an inward Na current flows and a regenerative depolarization ensues.

Refractoriness The behavior of the ionic fluxes described above can, in a general way account for the observed phenomena of refractoriness It has been stated that repolarization occurs because of inactivation of the inward transport of sodium and an augmented outward potassium current. Stated simply this means that during repolarization a stimulus (i e., applied cathodal or outward current) is made less effective because of (1) the opposing outward K^+ current and also (2) the unavailability of inward sodium current. Some further discussion of this material will be found in Chapter V a full explanation of the time course of sodium inactivation and changes in Na and K permeability may be found in the original descriptions (Hodgkin and Huxley 1952 b)

After potentials The giant axon employed for most of the studies of ionic fluxes cited above reveals only a positive after potential. This is associated with a phase of hyperpolarization of the membrane due to an increased outward potassium current. The elevated threshold of the "positive after potential" thus results from the increased requirement for stimulating current necessary to overcome the hyperpolarization. A negative after potential has not been seen in preparations suitable for the detailed studies required to reveal its basic cause.

Local excitatory state local response and accommodation The theory here discussed can account for several other phenomena observed in studies of excitable tissues. A local excitatory state will be created whenever the membrane potential is displaced towards zero by a subthreshold stimulus since the additional stimulus (cathodal current) required to reach the threshold potential is thereby decreased. The same subthreshold stimulus will result in a local response because the lowered transmembrane potential increases the inward sodium current and additional depolarization results. However the effect of the increase in Na permeability is soon overcome

by two factors, (1) the decrease of sodium permeability which accompanies an inward flux of this ion and which is often termed "inactivation" and (2) an increased K^+ permeability Consequently the membrane potential returns to normal values In a similar situation, when stimulus duration is prolonged, accommodation might arise from the same two factors inactivation of Na^+ transport and augmented outward potassium current.

OTHER THEORIES OF EXCITATION There is considerable disagreement concerning the mechanism by which many, if not all, of the phenomena associated with excitation are produced, furthermore, as will be seen in subsequent chapters, it is impossible to explain all of the proper ties of cardiac membranes strictly in terms of the theory just discussed

The role assigned to potassium in maintaining the resting potential has not been fully accepted and this portion of the theory has been opposed to some extent by Lorente de No (1947) on the basis of the observed slow depolarization of intact frog nerve trunk produced by this agent He similarly discounts the essential role of Na^+ in producing the upstroke of the action potential because of experiments in which the excitability of B and C fibers of the intact frog nerve could be maintained in the absence of sodium by means of tetraethylammonium ions and other quaternary compounds (Lorente de No, 1949) His experiments on the effect of anoxia and metabolic inhibitors (1947) stress the importance of oxidative metabolism, (1) in maintaining the membrane potential and (2) in producing accommodation by means of an active opposition to forces tending to depolarize or hyperpolarize the membrane (Lorente de No, 1946, 1947) Some of these conclusions of Lorente de No are at variance with results obtained from de sheathed nerves, where trapping of ions by the nerve sheath is prevented (Feng and Liu 1949 a and b, Huxley and Stampfli, 1951, Shanes and Berman, 1953)

The role of acetylcholine in excitation has been stressed by some workers (Nachmansohn and Wilson, 1951) who envision a combination of this substance with receptor protein as a necessary preliminary to changes in permeability of the membrane to sodium ions Furthermore, extensive studies of the effect of microinjections of various ions inside squid nerve (Grundfest et al , 1954) have resulted in a series of findings which are not explicable in terms of the ionic theory discussed above and which emphasize the role of active metabolic sodium extrusion

SUMMARY

The explanations which we have given of the processes involved in excitation and conduction are the ones most generally accepted The use of ionic flux and membrane pumps has permitted construction of an hypothesis quite pleasing to many neurophysiologists Addition of a role for acetylcholine has satisfied other individuals. Experimentation in this field has been cleverly conceived skillfully executed and the results very adequately reported. Unquestionably the facts of observation can be accepted Explanations and theories of function are quite another matter and it is anticipated that they will be modified very frequently in the future

Some of the seeming contradictions in theory and result have been explained but the basic processes involved in excitation and conduction are still not completely understood The fact that movement of ions across the membrane occurs during activity does not indicate that all phenomena of excitation and response are explained by these electrochemical reactions. The observations that excitation can occur in the absence of extracellular sodium and that other substances and influences can be substituted for this electrolyte do not demonstrate that the sodium shift is not important to and normally involved in excitation and conduction Ions must be present to participate in the current flow known to occur certainly no other mechanism of current flow has been demonstrated as yet in biological material.

Unquestionably metabolic processes enzymatic actions and chemical change are essential to membrane function The terms "pump" "carrier , may give a very unsatisfactory picture of processes involved in membrane activity but their use has permitted construction of a remarkably satisfactory description of the phenomena of excitation and response Just what constitutes this pumping" activity will probably be eventually determined and other perplexing questions will be resolved in the near future. For the present the important point to emphasize is that the functions of living tissue are carried on by a complex series of interrelated complementary and supplementary reactions and it will not be surprising if it is found that there is more than one chemicophysical pathway which the excitatory processes may take in depolarizing a cell membrane and evoking cell responses

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and time-course of excitation and recovery in that tissue far beyond the understanding of the same processes in cardiac muscle. Neurophysiologists had also demonstrated the many advantages provided by the use of certain electronic techniques It was thought that a reappraisal of the excitability cycle of the heart, employing similar methods of stimulation and recording might add considerably to the understanding of many of the phenomena revealed by earlier studies and might also help to elucidate the nature of the obvious differences between the recovery of excitability in nerve and cardiac muscle.

GENERAL OUTLINE OF TECHNIQUE

INSTRUMENTATION The excitability of the heart is conveniently expressed in terms of the strength and duration of the electric current pulse needed to produce an extrasystole However for this determination to have any meaning the instant in time during the cardiac cycle at which the test pulse is applied must be known i e precisely how many milliseconds after the onset of systole the test stimulus reaches the heart. In these studies an oscilloscope was employed in conjunction with suitable recording circuits so that the long persistence screen of the tube (12GP7) gave a record of the stimulus location in the cardiac cycle and at the same time electrocardiographic indication of the presence or absence of evoked extrasystoles The oscilloscope sweep was arranged to show a single electrocardiographic complex at a fixed location on the screen This was accomplished by triggering the oscilloscope sweep circuit from the voltage of the spontaneously originating action potential or more frequently by a provision for the pulse originating the oscilloscope sweep circuit to trigger a stimulator driving the heart. By means of a delay circuit in the stimulator the actual position of the drive stimulus could be varied relative to the sweep so that any desired part of the electrocardiogram could be inscribed at zero time Similarly the position in time of the test stimulus could be varied at will with respect to the oscilloscope sweep The actual position of either pulse was marked on the sweep by an internally generated marking voltage which produced a small, sharp deflection on the oscilloscope trace

To measure time in the cardiac cycle two synchronized oscillators were arranged to display time marks at 10 and 50 msec intervals along the trace The appearance of the trace when all of these markers and an electrogram were present is shown in Figure 12 A, B The occurrence

III Methods of Studying Cardiac Excitability

Techniques and apparatus which have been used and can be employed in the study of cardiac excitability and response are described in sufficient detail to permit their use by others interested in cardiac physiology

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THE TECHNIQUES USED TO STUDY the excitability of the heart have progressed *pari passu* with advances in electronics and with the application of knowledge thus gained to the armamentarium of physiological research The earliest investigations were performed very simply, excitability being determined by means of induction coil shocks, condenser discharges or by application of direct currents The responses of the heart were recorded by simple myographic devices on smoked paper Time relations could be estimated in only a very rough way and the stimuli were applied more or less at random To this epoch belong the studies of Bowditch (1871), Marey (1876), McWilliam (1888), Gley (1889), Engelman (1895), Cushny and Matthews (1897), and Woodworth (1902) Even if primitive, these methods permitted the delineation of the basic pattern of the excitability of the heart and furnished the first evidence of the refractory period, latency of response, the 'all or nothing' law, etc Somewhat later more precise studies were made possible by the advent of more adequate procedures for recording the mechanical and electrical responses of the heart (Wiggers, 1925) The introduction of mechanical rotary devices to drive the heart and to time the testing stimuli yielded valuable results in the hands of numerous physiologists among whom were Wiggers (1925) and Lewis and Drury (1926)

The next advance in instrumentation brought electronic devices into use in the study of cardiac excitability (Hoff and Nahum, 1938 Harris and Matlock, *1947*, *Garcia Ramos, et al*, *1948*, *Green, et al*, *1952*, Delgado and Sikand, 1952) In all instances, however, electronic techniques were employed only to a limited extent, namely to furnish stimuli of known magnitude and duration or to control their timing The importance of the work just mentioned should not be minimized, however, studies of nerve had, at the same time, *advanced knowledge of the nature*

of the driven beat was located in the tracing in a position convenient for the application of testing stimuli and the recording of possible responses. Following satisfactory adjustment of the electrocardiogram the testing stimulator circuit was switched on and the positioning marker associated with the test stimulus was adjusted to fall at the desired interval in the cycle The system was arranged so that although the marker related to the test pulse appeared on every sweep the actual test pulse only appeared at every 6th to 12th sweep (depending on an adjustment) The actual application of a test shock was signalled by a mechanism giving an audible click. It was thus possible to avoid the accumulative effects of stimuli and also to avoid disorganization of rhythm by too frequent extrasystoles

The testing procedure employed can be described as follows. At a given interval of the cardiac cycle the strength of the test stimulus was gradually increased until an extrasystole was produced stimulus intensity was then decreased below threshold and subsequently elevated again by

FIGURE 13. Schematic diagram of stimulating and recording circuits. *Note* Points A A, B-B, etc., are connected.

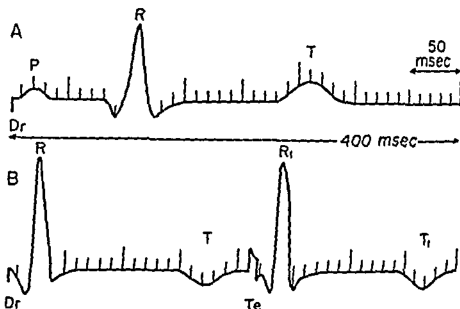


FIGURE 12 Electrograms as seen on monitoring oscilloscope A—Electrocardiogram obtained from indirect leads when driving stimulus is applied to the auricle B—Unipolar ventricular electrogram recorded when ventricle is driven directly Dr—Drive artefact Te—Test artefact

of an extra systole was of course easily seen as an additional complex on the trace The drive stimulus was a thyratron controlled condenser discharge while the testing shock was a rectangular pulse of adjustable strength and duration The testing current strength in milliamps was read on a second oscilloscope in terms of the voltage across a known resistor connecting the anodal electrode to ground, the animal was not grounded except through this known resistance Figure 13 shows in block form the general arrangement of the equipment. It can be seen that the drive pulse was applied through a transformer having small inter winding capacitance while the test shock was applied, without a transformer, directly from the plate of a constant current pentode tube

In making a test, the oscilloscope sweep was first set to repeat at a rate just a little higher than the intrinsic rate of the heart being studied The drive stimulus was then applied and increased in strength until the electrocardiogram complex recorded by the oscilloscope locked into position, i e, began to occur at a fixed interval after the signal of each driving stimulus, showing that the apparatus was controlling the heart. The drive pulse marker was then positioned so that the recorded complex

by intraperitoneal or slow intravenous injection The method of administration of the anesthetic had no detectable influence on the general condition of the animal nor on the subsequent course of the experiment. The possible effect of the anesthetic agent on experimental results was evaluated in a series of animals anesthetized with pentothal sodium during decerebration After the effect of this short acting anesthetic had disappeared, the excitability of the decerebrate dog heart was found to be similar in all respects to that of the anesthetized animal. In addition it was possible to show that whereas large rapid intravenous injections of pentobarbital did produce alterations in the experimental results intraperitoneal injections of 3 to 5 mg of this agent did not produce any detectable change. This dose is comparable to that periodically required during an experiment to maintain the desired level of anesthesia.

The surgical techniques employed in acute experiments require little description Early in this series the entire anterior chest wall was excised to ensure adequate exposure. Following attachment of the cardiac electrodes the chest was enclosed in a lucite box to prevent drying and cooling of the heart. After adoption of electrodes embedded in lucite plaques (see below) which assured perfect insulation of all contact, the surgical approach was changed to a sternal splitting procedure In these animals it was possible after placement of the electrodes to approximate the margins of the incision and continue the experiment with a virtual closed-chest preparation. Artificial respiration under positive pressure was provided and the tidal volume and rate adjusted to a level that was just sufficient to prevent spontaneous respiratory movements Routinely a slow intravenous infusion of isotonic saline was supplied. Blood pressure was recorded with a mercury manometer from the femoral or carotid artery and mean levels generally remained about 100 mm. Hg for 6 to 10 hours. Animals with mean pressures below 80 mm Hg were considered unsatisfactory for most experiments.

TESTING EXCITABILITY OF ARTIFICIALLY DRIVEN HEARTS

Decision to drive the heart at a fixed rate was made for several reasons and some of these are worthy of brief mention It was possible to let the heart beat spontaneously and then by means of signal-synchronization circuits to position the test stimulus at any desired interval after the R wave of the electrocardiogram However since the duration of the refractory period of heart muscle varies when rate changes, spontaneous changes

small increments until just adequate to elicit an extrasystole This effective current strength was then read in milliamps from the calibrated oscilloscope serving as an ammeter The stimulus strength was then lowered, the stimulus positioned at a new interval of the cycle, and the same procedure repeated During the relative refractory period threshold was measured at 5 msec intervals but later on in the cycle thresholds were determined only at intervals of 20 to 50 msec because experience had shown that shorter intervals of testing were unnecessary The accuracy of the timing or placement in the cycle of any threshold measurement made during the refractory period was ± 1 msec or better Generally, however, changes of less than 10 msec in the duration of the refractory period were not considered significant. It was likewise felt that any deviation from the trend of excitability change which did not have a temporal duration of 5 msec or more could not be identified with certainty

The calibrated oscilloscope employed to measure current flow during stimulation could be quickly adjusted to record in any of five ranges of sensitivity, 0 05, 0 20, 0 50, 0 200 and 0 500 ma Full scale movement of the recording beam occurred when the highest current flow *recordable at that setting was encountered Thus a great accuracy of* recording was obtained for stimuli of wide range of magnitude This oscilloscope was calibrated before use against several known current strengths for each range of sensitivity

In most experiments testing was begun late in diastole and then carried on progressively earlier in the cycle, however, similar results were obtained when the reverse procedure was employed By determining in this fashion the threshold for extrasystoles at 5 or 10 msec intervals throughout the entire cardiac cycle, a detailed plot of the cyclic excitability changes in heart muscle could be constructed This plot has been called the "strength interval" curve In addition, by leaving the time of application of the test shock in the cycle fixed and varying the duration of the stimulus a strength duration curve for any desired interval of the cardiac cycle could be obtained

SURGICAL PROCEDURES Mongrel dogs of all sizes and ages were employed in most of the studies of auricular and ventricular excitability Operative techniques similar to those which will be described for dogs were also used for cats, details of experiments on turtles, rats, frogs and other species will be mentioned in subsequent chapters

Animals were anesthetized with pentobarbital sodium, 30 35 mg/kg

range of pulse duration available was adequate to plot a complete strength duration curve and the peak output (approximately 100 times threshold) was sufficient to permit study of the recovery of excitability even early in the relative refractory period

In the preliminary stages of this work, the results with rectangular test shocks were compared with those obtained by means of test stimuli of a variety of shapes Condenser discharges thyratron discharges and induction shocks all gave results qualitatively similar to those obtained with rectangular pulses in mapping the course of the recovery of excitability in heart muscle

As stated previously the test stimulator was triggered in such a manner that test shocks were only applied to the heart at a sub-multiple of the driven rate Infrequent stimulation was employed so that any long lasting effect of a previous test would have virtually disappeared before the next stimulus was applied The 3 to 5 seconds between test shocks allowed in these experiments was quite adequate to eliminate any detectable effect of the test stimulus itself on the subsequent excitability of the heart muscle. An additional reason for this spacing of test shocks was that each extrasystole in turn produced a transient change in the course of recovery of the post-extrasystolic beats The technique of testing at inter vals of several seconds thus permitted the heart to re equilibrate at the driven rate before a subsequent threshold determination was made.

The stimulus strength was measured in milliamps across a resistance to ground The voltage required for stimulation was not employed as a criterion of excitability because of the unavoidable variations in inter electrode resistance associated with contraction and relaxation of the heart and because it is the actual current crossing the cell membrane that produces stimulation of irritable tissues.

STIMULATING VALUE OF THE TESTING PULSE It seems to be adequately established that for a cell to be stimulated electrically the stimulus must lower the potential across the membrane of the cell by a specific amount—about 15 per cent of the total membrane potential. It seems also to be necessary that this forced membrane breakdown must take place over a minimum area or the area of breakdown will recover without any spread or propagation What this minimum area is in the case of cardiac tissue has not been established If silver chlorided wire electrodes of the type discussed here are used their total surface area is of the order of several square millimeters, but of course this whole area

in cycle length would thus place the test stimulus at a different part of the excitability curve (even though the R wave to test stimulus interval remained constant) Consequently the accurate determination of the course of the recovery of excitability would be impossible Furthermore, the maintenance of a fixed cycle length facilitated the direct and immediate comparison of data during an experiment. This was especially desirable when other variables that normally change heart rate, such as vagal or sympathetic stimulation, were being studied In addition to these considerations, it was often convenient to study hearts at rates either faster or slower than the spontaneous rate present at the time of the experiment. To accomplish this, the S A node was crushed and then the heart driven by means of a rhythmically applied stimulus

DRIVING STIMULI The driving stimulus was biphasic in shape, (a thyratron discharging through a transformer was employed) and its strength was adjusted to a level approximately twice the threshold value The possibility that the driving stimulus itself would alter the subsequent course of recovery of the heart muscle was checked in the following fashion *In all experiments it was possible to study the excitability of the* spontaneously beating heart by triggering the test stimulus from the R wave and to compare these results with those obtained from the same heart driven at approximately the same rate by the driving stimulator (see Chapter 4) A second check was possible in studies of ventricular excitability, here the driving stimulus could be applied either to the auricle or directly to the ventricle In the former case the normal impulse *propagated over the A V conducting system gave rise to ventricular beats* Finally, in studies of both auricle and ventricle it was possible to compare the effect of a driving electrode located at a distance from the test area with that of a drive electrode close to the test site The conclusion reached on the basis of these checks was that, while the driving stimulus might produce a slight, quantitative change in the absolute magnitude of either the threshold or refractory periods, this effect was constant throughout a given experiment and no qualitative changes in the excitability cycle were caused by the direct effect of the driving shock

CONTROL OF THE TESTING STIMULI The test stimulus employed was a rectangular pulse, the amplitude and duration of which could be varied independently The stimulators employed could deliver pulse durations varying from 13 0 to 0 05 msec and had a maximum output of 30 to 40 ma with the usual electrode arrangement In all cases the

that if a certain current is flowing into the electrode, the pattern of its distribution will depend on the electrode area and shape only in the immediate vicinity of the electrode. At a short distance the pattern takes up the hemispherical shell shape described regardless of the original area and shape of the electrode. If the electrode develops a high resistance on its surface then the total current will be reduced but if by applying more voltage the total current is kept constant the location of the hemispherical surface where the most remote stimulation occurs is unaffected.

If the requirements for stimulation are for a current density of "a" milliamperes per square millimeter over an area of "b" square millimeters then we see that the requirement a x b gives the dimension of current alone and thus by measuring the current flowing into a small electrode we have a measure of tissue sensitivity which is relatively independent of electrode area for small electrodes and which is also independent of electrode surface resistance. If excitability remains constant the minimum current flow necessary to stimulate will also *remain constant*. If excitability should either increase or decrease more current or less current will be required for stimulation.

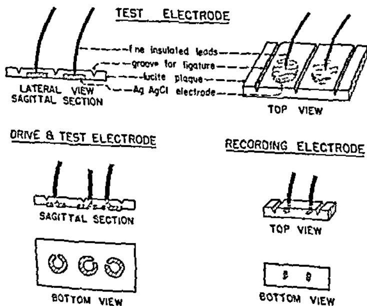


FIGURE 14. Sketch of electrodes employed in acute experiments.

does not make identical contact and it is probable that the main stimulating current enters the tissue from an area considerably smaller than this It is also likely that as the heart contracts there is some movement of the electrodes relative to its surface and so a further probability of variation of the current flow path

When current enters tissue it must distribute itself in a fairly complex way The interstitial fluid has a low resistance relative to the membranes themselves The cytoplasm in the cells also has a low resistance and comprises the major part of the tissue volume Thus current crosses the membranes and in doing so either increases or decreases the transmembrane potential depending on its direction of flow If a cell is lying transverse to a current flow one would expect one side of the cell to be depolarized while the other side is not There is always a current flow along the cytoplasm so that there exists the probability of the current densities across the membrane at different parts being different In a given area near the cathode current may leave the cells from all sides in sufficient strength to stimulate whereas current enters the cells further along their length in a more dispersed way This entry of current may partly strengthen the membrane potential locally or may not affect it to a significant extent

The overall current density in an area must have a certain minimum value in order to exert sufficient membrane voltage cancelling effect to stimulate From the theory in classical electricity concerning the spread of current in the earth from a rod or surface conducting plate it is known that the current will spread from its origin point so that not far from the origin approximately hemispherical "shells" of equal current density will be formed and the law of reduction of this density with distance states that the current is inversely proportional to the square of the distance In a limited volume of conductor this will not hold exactly When current is flowing from an electrode into a volume conductor such as the heart tissue, there will be at a certain distance a hemispherical shaped area where the current density will have been reduced to the minimum value at which membrane breakdown occurs Within the volume of this hemisphere all membranes may be broken down If, however, the total area of this hemispherical area of effective current concentration does not meet the 'minimum area" requirement for evoking a propagated response, no stimulation results

Referring again to the study of earth currents it can be observed also

first place the test stimulus artefact was usually large enough, at high stimulus intensities to partly conceal early extrasystoles Furthermore in studies of auricular excitability the auricular extrasystoles were often masked by the ventricular complex. The solution to the recording problem was achieved by employing small contiguous bipolar electrodes mounted in the same manner as the stimulating electrodes and attached directly to the epicardium. One or more pairs of electrodes could be attached to either auricle or ventricle and used either for monitoring the excitability studies or for measuring latency and conduction velocity Whenever a unipolar electrogram was required, one lead from each electrode was paired with a central terminal of the Wilson type (1934)

PERMANENTLY IMPLANTED ELECTRODES A number of experiments were conducted on dogs with chronically implanted electrodes attached to the right auricle and ventricle These electrodes were cast from liquid plastic and were of two types. One, employed to record the cardiac electrogram and record heart temperature, contained two silver contact electrodes and in addition a small copper-constantan thermocouple (Figure 15) The other type contained three silver electrodes and was used to drive and test the heart. Braided wire leads encased in extruded

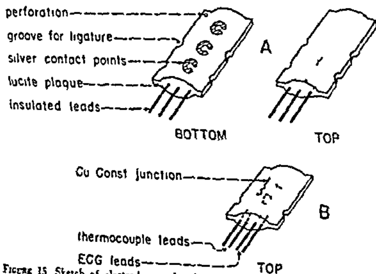


FIGURE 15 Sketch of electrodes employed in chronic experiments. A—Driving and testing electrodes. B—Recording electrode.

ELECTRODES AND LEADS The electrodes used for both driving and testing the heart originally consisted of silver wire loops 2 mm in diameter attached directly to the epicardium by means of three superficial stitches These electrodes were later discarded and in their place silver electrodes embedded in lucite plaques measuring approximately 5 mm in width by 2 mm in depth were employed The length of the plaque varied from 8 to 15 mm depending upon whether it contained 2 or 3 electrodes (Figure 14) The corners of the lucite plaque were attached to the epicardium by fine silk sutures The value of this technique was twofold, first, the electrodes made contact with completely normal muscle, the sutures through the epicardium remaining outside this test area and second, the contact of the electrode with the heart was more constant throughout the cardiac cycle With these electrodes, drying of the contact surface was minimized and threshold determinations remained remarkably constant over long intervals The number of stimulating electrodes employed varied in different experiments Normally three were attached to the right auricular appendage and three to the anterior surface of the right ventricle In each set the central electrode acted as a common anode for both the drive and test stimuli and the two peripheral contacts served as the drive and test cathodes With this set up it was possible to drive and test the auricle, drive the auricle and test the ventricle, or directly drive and test the ventricle The direct ventricular drive frequently produced some fall in blood pressure and was only employed when variations in A V conduction made the auricular drive unreliable

A great variety of electrode positions and relative placements was tried early in the course of these experiments The routine described here was that eventually selected because of its simplicity and because of the small number of contacts required All of the phenomena seen with this technique were also demonstrated when four separate electrodes (drive + and —, test + and —) were employed, regardless of whether these contact points were close together or widely separated

The procedure of chloriding the electrodes was usually followed, even though it was unlikely that this would appreciably influence electrode polarization, in view of the magnitude of the test shocks employed In practice, there was no detectable difference between the results obtained with bright silver and silver silver chloride test electrodes

The standard limb lead electrocardiogram was employed at the beginning of this work but proved unsatisfactory for several reasons In the

ventricle and by Draper and Weidmann (1951) on isolated Purkinje fibers had clearly demonstrated that this technique provided a graphic registration of the time course of depolarization and repolarization in heart muscle. It would thus permit better correlation between refractoriness and the degree of repolarization of the membrane between threshold and the magnitude of the resting membrane potential and would also supply additional information on such questions as latency local responses and pacemaker activity in heart.

Two different preparations were employed for microelectrode studies. In one the intact in situ dog auricle and ventricle were studied and in the other isolated fragments of dog rat, frog and other hearts could be used The in situ hearts were not ideally suited for exact quantitative determinations because of the great difficulty encountered in securing adequate immobilization however they did permit the study of normal myocardial activity and its physiological variations in an environment that had been minimally disturbed In isolated preparations, on the other hand, quantitative studies were more accurate and variables incompatible with survival of the intact animal could be investigated with ease

SINGLE FIBERS OF INTACT HEARTS In work on the intact heart the major problem of immobilization was handled in the following manner For experiments on the auricle the tip of a 1′ lucite rod ground to the size and shape of a small almond was inserted into the cavity of the chamber through a slit in the tip of the auricular appendage the slit subsequently being closed with a purse-string suture. The heavy plastic rod was then attached to the same rigid support that carried a pair of micromanipulators The tip of the rod inside the cavity of the auricle thus provided a rigid base against which the auricular muscle could be pressed and temporarily immobilized Mounted in the micromanipulators were the microelectrode an agar wick electrode and a tapered glass rod terminating in a loop 2 mm in diameter Before attempting to record with the microelectrode the glass loop was lowered so that it pressed lightly against the myocardium overlying the support in the cavity Just enough pressure was exerted by the loop to partly immobilize a small bit of tissue. The tips of the microelectrode and agar wick, which had been placed within the loop thus made contact with the surface film of liquid on the muscle The microelectrode was then lowered under direct microscopic visualization and penetration of a single myocardial fiber accomplished Following each successful impalement of a single fiber the

nylon were most satisfactory both from the point of view of breakage and tissue irritation In each animal a test electrode and a recording electrode were attached to both right auricle and right ventricle

Several aspects of the surgical preparation of these chronic animals seem to be of particular importance and are worthy of brief mention The heart was exposed through an incision in the fourth right intercostal space and the pericardium opened by a cruciate incision The electrodes were firmly attached to the epicardium of the right auricular appendage and anterior right ventricle with 5 0 or 6 0 silk and the electrode leads brought out through two small holes in the pericardium close to the base of the heart between the reflection of the pericardium on the right auricle and the phrenic nerve The initial incision in the pericardium was then carefully closed in such a fashion that constriction of the heart was avoided The thinness of the attached electrodes made this possible in all animals The electrode leads were then brought between the upper and middle lobes of the right lung to the back of the chest and passed through separate stab wounds in the intercostal muscles one and two inter spaces below the chest incision The chest was then closed in layers and the electrode leads made a sharp turn at each layer Finally, the leads were brought to the surface through separate stab wounds in the skin quite close to the midline of the back This path followed by the leads minimized any movement of the wires and served a dual purpose It prevented the introduction of infection along the course of the leads and also minimized breakage of the wires

Animals prepared in this manner required a minimum of post operative care A loose bandage and cotton jacket protected the leads between experiments and most animals gave satisfactory results for several months The details of the temperature studies employing these dogs are described in Chapter VII

EXCITABILITY OF SINGLE MYOCARDIAL FIBERS

During the course of these studies it became apparent that certain aspects of many projects were not within the scope of the techniques so far described for studying cardiac excitability Therefore, to supplement the measurement of excitability by means of test stimuli and the cardiac electrogram, work was commenced on the recording of transmembrane potentials of single fibers of the dog heart by means of glass capillary microelectrodes Similar work by Woodbury et al, (1951) on the frog

solution, oxygenated through a sintered disk with 5% CO_2 and 95% O_2, and maintained at a temperature of 38° C and a pH of 7.4. The composition of this solution (for dogs) was as follows NaCl 138mM, Dextrose 5.5 mM $NaHCO_3$ 12mM $CaCl_2$ 2.7 mM KCl, 2.7 mM, $MgCl_2$ 0.5 mM NaH_2PO_4 3.6 mM

Rhythmic contraction of the specimen was maintained at a constant rate by means of stimuli applied with a pair of pin electrodes Penetration of the cells by the microelectrode was accomplished under direct observation without further immobilization When desired, local unipolar electrograms were recorded from the surface of the tissue with a fine silver electrode surrounded by an air bubble to prevent shunting Pressure by the silver wire on the specimen was carefully avoided The indifferent electrode made contact with the bathing solution

In the case of the auricle, records were obtained from the endocardial surface of fragments of the auricular wall. The papillary muscle preparations were obtained from the right ventricle in some cases other groups of ventricular muscle fibers were used At all times only superficial cells were studied this was done to insure both adequate perfusion and oxygenation of the tissue and also rapid equilibration with any test substance

SUMMARY OF MAIN FEATURES OF THE TECHNIQUE EMPLOYED

To summarize the most important aspects of the techniques employed in the work on which this monograph is based the following points are listed

1) The excitability of the intact, in situ heart could be studied under reproducible conditions

2) Heart rate was controlled so that the duration of the cycle and thus the duration of the refractory periods remained constant.

3) Test stimuli could be applied at any desired interval of the cardiac cycle within an error of ± 1 millisecond and thus the exact threshold at any instant could be determined and checked at will.

4) This technique supplied constant rigid control of the intensity and duration of the testing stimulus with the possibility of changing independently any one of these parameters

5) The measurement of the current required to produce an extrasystole with a maximum accuracy of 0.01 ma., coupled with the ability to position the test stimulus at any desired millisecond after the driven beat, revealed

microelectrode assembly and loop were elevated to relieve the pressure on the underlying muscle and after several recordings from a given area the loop was moved to a fresh location

To immobilize the ventricle a small two pronged fork with blunt tips was inserted either into the cavity of the right ventricle or into the wall of the left ventricle 2 3 mm below the epicardial surface When this supporting structure was inserted, all visible vessels were avoided and an attempt was made to pass the tips between muscle bundles in order to avoid damaging the myocardium

The microelectrodes, of the type devised by Ling and Gerard (1949) were pulled from soft glass capillary tubing to a tip diameter of less than one micron and filled with filtered 3 M KCl by boiling under intermittent pressure Each electrode was examined before use to check on both the tip diameter and the absence of bubbles and then mounted in the micro manipulator Chlorided silver spirals were employed to lead from the 3 M KCl in both the microelectrode and agar wick which served as the indifferent electrode for the microelectrode circuit

Recordings were made with a cathode follower and D C. amplifier giving several inches of deflection on a switched beam long persistence 12 inch oscilloscope The cathode follower was of the miniature electro meter triode type having a grid current of less than 10^{15} amp which with a 100 megohm grid resistor gave no appreciable base line shift when switching from input open to input short circuited A standard 100 mv source was placed in series with the lead from the indifferent electrode to the cathode follower so that a calibration taking into account the needle resistance could be made at any time Electrode resistances of the order of 10 megohms were usual, with the average needle the overall time constant of the recording system was of the order of 250 micro seconds

SINGLE FIBERS OF ISOLATED MUSCLE PREPARATIONS Isolated tissues were all handled in approximately the same fashion and a description of the technique used for the dog heart with minor modifications applies to all others Dogs were anesthetized as above, and the chest opened under artificial respiration The tissue to be employed was not removed from the heart until just before use, less than one minute elapsing between the time it was severed from the heart and its immersion in an oxygenated modified Tyrode solution The specimen was pinned under slight tension to a paraffin block immersed in 100 ml of circulating

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even minor changes or fluctuations in the course of the recovery of excitability

6) The drive and test electrodes made constant contacts with normal uninjured tissue

7) The direct recording of the auricular and ventricular electrogram by means of contiguous punctate electrodes clearly revealed the presence or absence of any electrical response and permitted accurate measurements of latency and conduction velocity

Other details of the methods used will be given as this becomes necessary in the description and discussion of results obtained in the specific studies dealt with in this monograph

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EXCITABILITY CYCLE OF THE VENTRICLE

METHODS OF STUDY Two somewhat different methods were used in determining the level of excitability of the heart during diastole and in studying the time-course of the excitability changes associated with activity The first of these involved measurement of the threshold intensities for stimuli of a wide range of durations *Strength-duration curves* were then plotted and the rheobase and chronaxie obtained at each interval of the cardiac cycle thus determined The second method merely required the use of a stimulus of fixed duration and the determination of the threshold strengths required to evoke a propagated response at various intervals of the cycle A plot of the data thus obtained was called a *strength interval curve* In the experiments to be described, both procedures were followed A few other details of the experimental methodology should be given however, prior to a discussion of results obtained

A rigid control of the parameters of the test stimulus is of primary importance in a study of excitability This was accomplished by using electronically formed rectangular pulses of known duration (0 1 to 13 msec.) and by reading threshold current strength from a monitoring oscilloscope (see Chapter III) carefully calibrated to give accurate readings from 0 01 to 50 0 ma. Accurate placement of the test stimuli at selected intervals of the cardiac cycle is also essential. This required precision was obtained by triggering the test pulse from either the R wave of the spontaneously originating electrogram or from the driving stimulus The latter procedure is preferable because the perfectly constant driving rate of an electronic stimulator eliminates the variations in the time-course of recovery which necessarily accompany any minor alterations of the spontaneous cycle length. The equipment used in this work permitted positioning of the test stimulus in the cycle with an accuracy of ± 1 0 msec. A final factor of importance is the correct recognition of the response of the heart to test situations Multiple bipolar electrograms recorded on a 12 oscilloscope were found most suitable for this purpose

Studies of the recovery of normal cardiac excitability after a driven beat were carried on in the following manner The excitability of the ventricle as defined in terms of the thresholds to stimuli of several durations was determined at selected intervals of the cycle from the end of the absolute refractory period to late diastole The threshold was considered to be that minimal current strength which elicited a propagated

IV The Excitability Cycle of the Heart

The changes in cardiac excitability which occur with each beat of the heart are defined Refractoriness and the irresponsive periods are considered and some newer phenomena, "the dips," which occur during the recovery of normal excitability are described and their significance discussed The normal excitatory process the mode of action of various stimuli, supernormality and other matters pertinent to understanding of the cyclical behavior of the ventricle and auricle are dealt with

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THE EXCITABILITY OF THE HEART does not remain constant. It changes as neural and humoral influences act upon the heart and it also undergoes major modifications during the cardiac cycle Before considering the peculiarities of excitability shown by the myocardium during different phases of cardiac activity it should be pointed out that there is a regular sequence of electrical and mechanical events consequent to the origin of each heart beat The cycle begins with the initiation of activity in the sino auricular node Subsequently a wave of depolarization sweeps over the auricles and then the ventricles and initiates a series of mechanical events within these organs The muscular elements of the auricles contract bringing these chambers into a state of systole As the auricles complete their mechanical activity and even before they have attained complete relaxation the ventricles start their contraction The resulting ventricular systole has been divided into two phases while four phases of subsequent diastole are recognized (Wiggers, 1928, 1952) It is possible either to think in terms of a cycle of electrical events identifiable by electrocardiographic recording or in terms of a sequence of associated reactions which can be recorded mechanically Chapter XI will be devoted to a consideration of contractile phenomena and the relationship of mechanical events of the cycle to changes in excitability of the heart In the present chapter attention is centered on the testing of excitability of the auricle and ventricle by determination of the threshold strengths of stimuli which evoke propagated electrical responses at various intervals of the cardiac cycle

action potential. A strength-duration curve was plotted for each interval of the cycle at which tests were made. Strength interval curves were also plotted for each test shock duration. This was done by indicating current strength used to produce a response along the ordinate and the intervals of the cycle at which tests were made (after the upstroke of the R wave of the driven beat) along the abscissa Figure 16 shows examples of both types of curve for the auricle and ventricle of the dog heart. It should be noted that a progressively condensed scale was employed for the ordinates of the strength interval curves because of the wide range of stimulus intensities employed.

The production of ventricular fibrillation has, in the past, frequently complicated studies of ventricular excitability In the present series of experiments this was avoided by gradually increasing the stimulus in tensity until it was *just adequate* to elicit a single extrasystole. In this way it was possible to avoid fibrillation even when testing during the vulnerable period of the cardiac cycle because no period was ever found during which the minimum effective stimulus produced fibrillation in a normal heart (see Chapter VI)

STRENGTH DURATION CURVES The ventricular strength-duration curves (Figure 16-A) representing the state of excitability at sequential intervals of the cardiac cycle appear to be of two different types There is a low intensity group obtained late in the cycle and a group produced by high intensity stimuli characteristic of the early phases of the cycle (Orias et al. 1950) At certain intervals the curves demonstrate a sudden transition from the low threshold type to the high threshold family These breaks in the strength-duration curves are merely an in dication of the fact that during the relative refractory period long-dura tion stimuli are much more effective than pulses of short duration This selective sensitivity to different durations of stimuli will be discussed later in relation to the definition of the boundaries of the refractory periods and the creation of long lasting excitatory states

Inspection of these strength-duration curves reveals that the thresholds for long duration shocks are very much lower than for stimuli of brief duration If however the total current flow required to stimulate the heart at any one interval is calculated, the shorter pulses are found to be more effective in terms of microcoulomb requirement (Lassalle 1928 Brooks and Suckling 1951) The difference in relative effectiveness can perhaps be explained on the basis of a greater degree of accommoda tion to stimuli of long duration

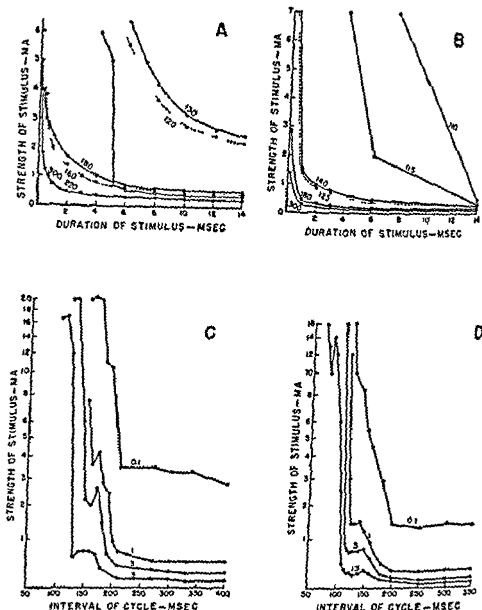


FIGURE 16 Strength duration curves of dog ventricle (A) and auricle (B) *Lowest curve repre ents excitability during late diastole* The numbers *on each curve identify* the interval of the cycle during which the particular strength duration curve was obtained *Dotted curves obtained during dip intervals* Certain curves (o——o) show abrupt *transition from low to high thresholds* Strength interval curves of dog ventricle (C) and auricle (D) showing the time course of recovery of excitability as determined by stimuli of 0 1 1 0 3 0 and 13.0 *msec duration Note* (a) *different durations of ab solute and relative refractoriness as indicated by the different durations of stimuli* (b) *all stimuli give a similar identification of the end of total refractory period and time of occurrence of dips* Primary or early dip detectable only by long duration stimuli

and irregularities in the recovery of excitability can be clearly seen These transient irregularities are manifest as one or more dips in each curve.

The strength interval curves show threshold to stimulation which is the reciprocal of excitability A more direct representation of changes in cardiac excitability would be given if the reciprocals of these threshold values were plotted If this were to be done the threshold value for excitability during diastole when a steady level is maintained would represent 100 per cent recovery or normal excitability Curves of this sort would represent the "dips" or periods of unsustained recovery as humps It is unnecessary however to express excitability in this direct manner in most instances because it has become customary to describe excitability in terms of threshold requirements It should be remembered, however that the strength interval curve represents stimulation thresholds and these vary in the opposite direction from excitability

Strength-duration and strength interval curves show the changes in cardiac excitability which occur following each beat of the heart. Four phenomena of ventricular excitability revealed by these curves are deserving of as close an analysis as can be made at the present time. These are 1) refractoriness 2) supernormality 3) latency of response and 4) the "dip" phenomenon

THE REFRACTORY PERIODS

ABSOLUTE REFRACTORY PERIOD The absolute refractory period by definition is the interval of the cardiac cycle during which stimuli are ineffective in that they *fail* to elicit propagated electrical responses. The concept of an absolute refractory period implies the existence of two finite boundaries one coincident with the *onset* of depolarization and the other occurring during repolarization separating the end of the absolute from the onset of a relative refractory period The relative refractory period in turn is that *interval* of the cardiac cycle during which only stimuli of greater than diastolic threshold strength will succeed in eliciting a propagated electrical response

The results of studies of cardiac excitability performed on exposed hearts of dogs and other animals and on chronic preparations with implanted cardiac electrodes require some modification of these concepts of refractoriness The terminal boundary of the absolute refractory period cannot be readily determined When for example rectangular pulses of

The most striking phenomena shown by such families of strength-duration curves can be seen in Figure 16 A At two intervals of the cardiac cycle, at 120 and again at 160 msec after the R wave of the driven beat, the threshold for each stimulus duration is actually lower than required at immediately succeeding intervals (130 and 180 msec after driven beat) although a longer period had elapsed for progression toward recovery of normal excitability The position of these two curves to the left and at lower intensity levels, in whole or in part, than those obtained later in the cycle represents an irregularity in the progressive recovery of excitability This displacement of the strength duration curves indicates a transient increase in the excitability of the heart to test stimuli as compared to the levels prevailing just before or immediately after the particular intervals noted Either a degree of recovery of excitability occurs momentarily which cannot be sustained or processes occur periodically which reverse the trend of recovery The observed result would be the same in either case

This reversal of the expected position of certain strength duration curves occurs only during the relative refractory period but has been found in the large majority of hearts studied and in all species of animals *which have thus far been used (i e dogs, cats and turtles)* The finding indicates an actual irregularity in the recovery of excitability which is even more clearly shown by strength interval curves

Finally, it should be pointed out that the shapes of the strength duration curves and the varying positional relationships between them indicate that the determination and use of chronaxie alone (*Lapicque and* Fredericq, 1924) as a criterion of excitability might be misleading under conditions such as these Calculations of the chronaxies in this series of strength duration curves (Figure 5 C) show that for specific intervals, the chronaxie does not always reveal the state of excitability indicated by the position of the total curve Others have likewise concluded that chronaxie alone is an unreliable expression of the state of cardiac excitability (Wegria and Wiggers, 1940)

STRENGTH INTERVAL CURVES Figure 16 C shows a family of ventricular strength interval curves obtained in one dog These curves best portray the sequence of changes in excitability which occur throughout the cardiac cycle The presence and duration of an absolute and relative refractory period can be perceived at a glance and the *fluctuations*

1950) Test stimuli applied to the ventricle very early in the cycle did have an effect directly on this chamber and created therein an excitatory response ultimately giving rise to a conducted impulse On the basis of these experiments it has been concluded that in cardiac muscle as in nerve there is an absolute refractory period but that in some cases this period as in nerve, is very brief and may include only the rising phase the period of overshoot and at most, only the earliest few milliseconds of the repolarization phase of the action potential.

After depolarization cardiac muscle recovers much more slowly than does nerve and the threshold remains very high for a much longer time Stimuli which are only five to ten times the strength required to stimulate during diastole reveal a very definite absolute refractory period one which is much longer in duration then the phase of depolarization over hoot and earliest repolarization As has been stated before when very strong stimuli (up to 30 ma. and of 10-15 msec. duration) are used there is in ome hearts practically no absolute refractory period how ever in these instances the immediate effects of the stimulus are probably quite different from those of the test shocks employed to excite the heart in diastole or during the late phases of the relative refractory period The nature of the long lasting effects of very strong stimuli is not as well known as are the processes involved in excitation by more nearly phy iological strengths of stimulation (see discussion of latency below)

RELATIVE REFRACTORY PERIOD The relative refractory period has been described as that period during which the excitability of cardiac muscle increases rapidly and then more slowly until the resting level is attained Figure 16-C and D demonstrates graphically the time course of this recovery of excitability in both ventricular and auricular muscle As seen the restitution of full excitability is not a smoothly progressive process as the test stimulus is moved later and later in the cycle excit ability increases rapidly then decreases slightly increases again at a rapid rate, then decreases once more and finally increases slowly until the resting level is attained. These fluctuations or "dips" of excitability to test stimuli during the recovery phase will be analyzed later in this and subsequent chapters

TEMPORAL RELATIONSHIP BETWEEN ABSOLUTE AND RELA TIVE REFRACTORY PERIODS When the excitability of the ventricle is tested throughout the cardiac cycle by application of test pulses of different duration, the strength interval curves thus obtained clearly dem

0 1 msec duration were employed with current strengths varying from 0 to 20 ma as testing stimuli, the terminal boundary of the absolute refractory period of the driven beat was located 160 msec after the onset of depolarization in the experiment from which Figure 16-C was taken When a stimulus of 3 0 msec duration was used, the maximum stimulus strength available (20 ma) failed to produce extrasystoles only when applied earlier than 145 msec. after the onset of depolarization Similarly, when the duration of the test stimulus was increased to 13 0 msec the terminal boundary of the absolute refractory period was found still earlier in the cycle, at 100 msec after the onset of depolarization These results demonstrate that the duration of the absolute refractory period and the duration of the relative refractory period as well, are dependent upon the parameters of the test stimulus employed As seen in Figure 16 C and D, this has been found true in the case of both ventricular and auricular muscle (Orias, et al, 1950, Brooks, et al, 1950)

Although the maximum stimulus employed did not exceed 13 msec in duration and 30 to 40 ma in strength in some normal hearts practically no absolute refractory period was revealed In several experiments a test stimulus applied as little as 10 msec after the onset of depolarization was effective in that it produced, although after considerable latency, a propagated extrasystole Similar results have been reported for the isolated cat auricle and papillary muscle (DiPalma and Mascatello, 1951)

This problem of the identification of the boundaries of the absolute refractory period is an old one and in Chapter I mention was made of Marey's (1876) conclusion that a period of absolute refractoriness is very brief if actually existent Hildebrand (1877) and Woodworth (1902) postulated that Marey's results were due to excitation of the auricle by stimuli thought to act very early in the ventricular cycle In the recent experiment cited above, however, the possibility that very early testing stimuli produce a ventricular response due to direct stimulation of the auricle was ruled out in the following manner In the first place, a similar very brief (10 20 msec) period of absolute refractoriness was occasionally found to exist in the auricle when strong, long duration (10-13 msec) shocks were used to determine the limits of auricular refractoriness (Brooks, et al, 1950) and this could not be due to stimulation of another structure Secondly, the use of multiple bipolar recording electrodes applied to both auricle and ventricle permitted the exact localization of the origin of the propagated electrical response (Orias, et al

quently the sensitivity and recording scale of the calibrated oscilloscope used for measuring the strength of threshold stimuli was modified to permit detection of very small changes of current flow at low intensities of stimulation Following this improvement in technique a phase of supernormality frequently was found immediately following the end of the refractory period. This supernormality lasted for 50 to 200 milliseconds and during this interval the threshold was often 5-15 per cent lower than later in the cycle (Figure 17) Nevertheless, supernormality often consisted of a change in threshold of only 0 01 to 0 05 ma Such a change could not have been detected by most methods previously employed and it is not surprising that results have been somewhat contradictory This conclusion, that there is a phase of supernormality immediately following the refractory period is supported by the work of Weidmann (1955) on single isolated Purkinje fibers of the sheep heart. During the terminal phases of repolarization he found a brief period during which a smaller current pulse than was required later in the cycle could give origin to a propagated response More will be said of this in Chapter V which deals with functions of individual cardiac cells

The supernormality referred to here is a supernormality with respect to the threshold to stimulation later in diastole. There are other periods of relative supernormality during which stimulating current requirement is less than at a preceding and subsequent interval. The occurrence during the relative refractory period, of oscillations ("dips") in the strength interval curves depicting the recovery of excitability suggests that the supernormality occurring at the end of refractoriness might be merely the terminal phase of the oscillatory process creating the "dips" during the relative refractory period (Figure 17) At any rate, supernormality, though present, is not a conspicuous phenomenon in the excitability cycle of the dog ventricle Furthermore no evidence has been found to indicate that the heart is vulnerable to fibrillation during this temporary phase of hyperexcitability (see Chapter VI)

LATENCY OF RESPONSE

The phenomenon of latency of response has been discussed rather briefly in Chapter II Even when the response of an excitable tissue is recorded from the actual site of stimulation, there is a time delay (latency) between application of a threshold stimulus and appearance of the evoked action potential. It is difficult to place electrodes at the exact area on a

onstrate that the duration of the total refractory period (absolute plus relative) as delineated by all durations of stimuli is quite constant for any given heart rate (Figure 16 C and D) Although stimuli of long duration show a brief phase of absolute refractoriness the relative refractory period is correspondingly long while stimuli of short duration indicate that the absolute refractory period is very long and the phase of relative refractoriness is correspondingly shorter The subdivision of the refractory period into phases of absolute and relative refractoriness, therefore, is somewhat arbitrary However, the entire period of subnormal excitability (the total refractory period), which corresponds to the time required for complete restoration of normal excitability is uniformly identified by stimuli of all durations

SUPERNORMALITY

A long interval of supernormal excitability immediately following the relative refractory period was found by Adrian (1920) in the frog ventricle when the fluid bathing the tissue was acidified This was the first time that a period of supernormal excitability was reported for the heart and also the first time that the term was used in this connection In isolated quiescent apical preparations from frog ventricles Wastl (1922) could not always find a supernormal phase, when present he ascribed it to an increased acidity Hoff and Nahum (1938) experimenting on cats, found a supernormal period always present in animals anesthetized with barbiturates but only a very small proportion of decerebrate animals (two out of nine) showed a very shallow supernormal period On the clinical side a supernormal period of excitability has rather frequently been postulated to account for early extrasystolic beats (Lewis and Master, 1924, Scherf and Schott, 1939, Smirk, 1949) However, other explanations have been offered for such premature contractions (Wenckebach and Winterberg 1927 Wolferth, 1928) Other investigators (Lewis and Master, 1925, Sikand and Nahum, 1952) failed to find "supernormality" in the dog heart Supernormality was not a conspicuous feature of the excitability cycles of the hearts of cats and turtles (Hoffman, et al, 1951) It seems that there always has been some doubt as to whether a supernormal period actually exists under normal conditions

Very little evidence of supernormality was found by the present writers in early studies of the dog's heart (Orias, et al, 1950) Subse

membrane where a stimulus induced reaction will first occur Such electrode placement if accomplished introduces difficulties of recording because of interference by stimulating current (stimulus artefact) It is the usual procedure to record the tissue response at a point some distance from the site of application of the stimulus. Therefore, the latency between the time of application of the test shock and the appearance of the *propagated* action potential at the recording leads is composed of a very short true latency and a longer conduction time. If another aspect of tissue response such as muscle contraction is utilized as a signal of the occurrence of activity the apparent latency will be still longer (Wiggers 1925)

In the experiments performed to determine the excitability of the dog heart the latencies of the electrical responses were measured The action potentials of auricle and ventricle were recorded from multiple pairs of contiguous punctate, bipolar electrodes. Such electrodes are least influenced by stimulus artefact and are thought to be best suited for timing the arrival of activity (Harris and Moe, 1942) In most experiments three pairs of these electrodes were attached to the surface in such a sequence as to lie in a straight line from the stimulating electrodes The nearest recording pair was approximately 5 mm. from the site of stimulation and the other pairs were 10 and 20 mm. farther away This arrangement permitted easy measurement of the time elapsing between application of the stimulus and appearance of activity at each pair Measurements of distances and conduction time permitted estimation of "true latency" from the latency due to conduction.

It was found that latencies of response vary greatly during the cardiac cycle Figure 18-A and B shows that throughout diastole a time when the level of excitability is constant, the overall latency between test artefact and propagated response is unchanged As the test stimulus is positioned earlier and earlier in the relative refractory period however the response lags farther and farther behind latency becoming progressively longer Perhaps the most interesting point is that all responses to stimulation during the relative refractory period occur at approximately the same time in the cycle as though there is a definite interval in the cycle before which a propagated response cannot occur This limit has been found to correspond to the end of the total refractory period and the T wave of the simultaneous electrocardiogram (Orias et al., 1950) One additional observation has been that the latency between stimulus and

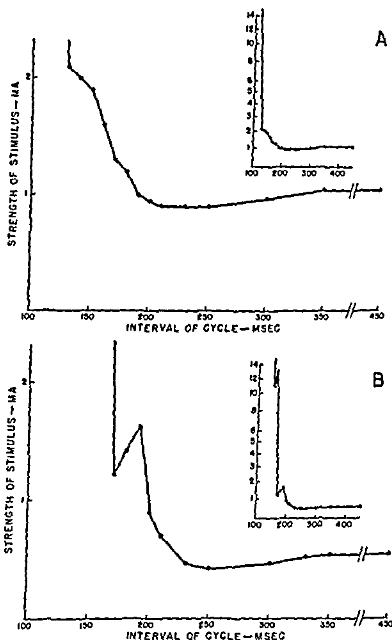


FIGURE 17 Strength interval curves of auricle (*A*) and ventricle (*B*) showing expanded segment revealing supernormality Inserts are complete curves from which expanded portions were taken

response is most often changed when the effective test pulse is applied during the "dip" in the strength interval curve

LATENCY AND A LOCAL RESPONSE The effectiveness of stimuli acting during the period of subnormal excitability depends on their ability to produce an effect which will *eventually* give origin to a propagated action potential. It has not been possible as yet, to study the local changes in cardiac muscle in the immediate vicinity of the testing electrodes during situations when latency is increased However, inspection of the data in Figure 19 permits certain conclusions The curves depicting time lapse between the test shock and arrival of the response at each of the two pairs of recording electrodes are almost parallel throughout the entire cycle This demonstrates a constancy of conduction velocity

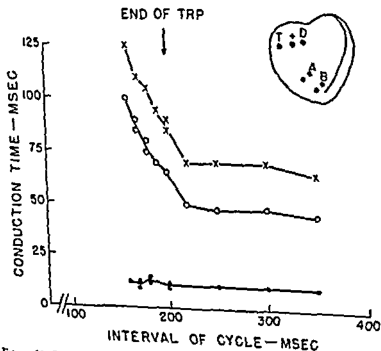


FIGURE 19 Graph depicting conduction time from test el ctrodes (T) to a near (A) and distant (B) *pair* of recording electrodes. The times to A (o——o) and to B (x——x) increase proportionately as the stimulus is advanced into the refractory period. Interelectrode conduction time (•——•) remains constant. Insert shows ar rangement of electrodes on heart. Driving cathode (D)

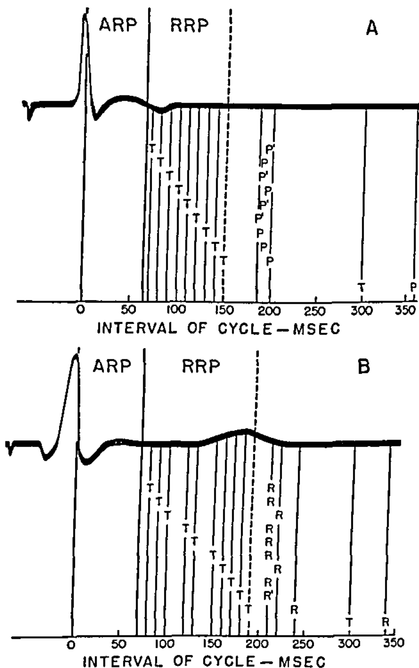


FIGURE 18 Tracings of auricular (A) and ventricular (B) electrograms showing temporal relationships of the refractory periods to electrical activity (ARP absolute and RRP relative refractory period) Also shown is the progressive increase in latency to stimuli (T) placed progressively earlier in the relative refractory period Time of response to stimuli indicated by P' (auricle) and R (ventricle) Test at 300 msec. shows latency of response after full recovery

stead of just prior to the "break" of the test stimulus as presumably would be the case of threshold stimuli

IRRESPONSIVENESS VERSUS REFRACTORINESS AND SUBNORMAL EXCITABILITY

Consideration of the refractoriness of the heart to stimulation and the prolonged latency of response to stimuli applied during the total refractory period has led to use of the term *irresponsive period* In order to produce a propagated response stimuli applied during this period of refractoriness or subnormal excitability create a local effect which persists until the myocardium has recovered sufficiently to give origin to a normally conducted wave of excitation A similar period of delayed or suspended response in nerve and skeletal muscle was demonstrated by Lucas (1909) He originally called this the "irresponsive period" but after expanding his observation to the heart of amphibians he criticized and discontinued the use of his own nomenclature He pointed out that such a name is not satisfactory because it does not indicate the essential feature of the phenomenon which is a *delay of response* until a fixed moment rather than a complete failure of response to occur (Lucas, 1910)

When one begins to consider what may actually be happening in the heart following initiation of a beat it becomes apparent that most current nomenclatures are somewhat inadequate. Numerous terms have been used to describe the characteristics of that phase of the cycle subsequent to the initiation of an action potential (Drury 1936) The effective refractory period" the "full recovery time" the premature response interval the "period of subnormal excitability and the "total refractory period have been employed and this period might also be called a phase of subnormal conductivity" a period of "suspended responses" or an adromatropic period etc None of these is absolutely correct in the strictest sense they are descriptive and perhaps correct within limits but little is gained by the endeavor to supplant older terminology with words which possess similar limitations *It is* certainly true that a refractory period or a phase of subnormal excitability occurs This is also an irresponsive period since a *normally* propagated response cannot occur until the heart has recovered its excitability and the capacity to propagate a response in the *normal fashion* In terms of localized effects however, stimuli do create excitatory states which may constitute in some instances a local response and it is probably true that there is even some

and indicates that the increase in latency takes place before the impulse has reached the recording electrodes nearest to the test site

There are two possibilities which might explain the delayed arrival of activity at the first recording point when stimuli fall in the relative refractory period First, the stimulus might create a persistent change in the myocardium during the relative refractory period which lasts long enough to elicit a propagated action potential after excitability has been *completely restored This would be an increase in true latency* Secondly, the test shock might actually produce an immediate but very slowly conducted response during the relative refractory period Due to this marked slowing in conduction, the myocardium somewhat distant from the stimulating electrodes would reach a fuller degree of recovery before *activation by the slowly traveling action potential* Eventually, the action potential would encounter fully excitable tissue and the conduction velocity would return to normal The increase of latency in this latter case would be due to the well known slowed conduction in partially refractory tissue (Gasser and Erlanger, 1925, Rosenblueth, 1941)

Whether the observed latencies result from one or the other or a combination of both these effects cannot be stated at this time It is reasonably *certain, however, that stimuli which have an eventual effect*, even when applied only a few milliseconds after the onset of activity, must create some sort of a very long lasting state Immediate production of an action potential early in the refractory period has not been demonstrated and in some instances latency lasts almost as long as the entire electrical systole of the myocardium Other investigators have similarly demonstrated that the excitatory effects of long duration high intensity stimuli can outlast the refractory period (Forbes, Ray and Griffith, 1922, Moe, Harris and Wiggers, 1941) and even result in repetitive firing (Lucas, 1911, Katz, 1936, Rosenblueth, 1941, Orias et al, 1950) Whether these long lasting effects result from tissue polarization, transient injury, or some other effect, has not been determined

Stimuli stronger than the threshold value for the particular instant of the refractory period under investigation tend to shorten the latency of the propagated response This might be due to 1) a greater spread of current and a stimulation of tissue nearer to recording leads, or 2) a more rapid reduction of the membrane potential to a level of instability thereby tending to start propagation of activity nearer the "make" in

relative refractory period Stimuli of long duration (10 msec.) usually reveal one major late dip and one or rarely two earlier ones (see Figure 16-C and D) These fluctuations can be described in the following manner Stimuli near maximal strength (30 ma) often produce a response during a 10 msec. interval early in the cycle but fail to do so when placed a few milliseconds later the heart again becoming absolutely refractory Ten to twenty milliseconds still later in the cycle maximal stimuli may be effective once more suggesting a second recovery of excitability Characteristically there then follows a quick extensive recovery of ventricular excitability which brings the threshold almost to normal. A subsequent increase in threshold then occurs lasting for 20 to 40 msec. before threshold determinations indicate the attainment of full excitability characteristic of normal diastole. The term "dip" is employed to designate the intervals of *increased excitability* this emphasis is made because of several other interesting properties associated with the enhanced excitability The early or high threshold "dip" is demonstrable in the majority of experiments and the late low threshold "dip" is present almost without exception

Under constant conditions of excitability stimuli *of different* durations reveal these dips at the same positions in the cardiac cycle. However strength interval curves obtained by means of very short duration stimuli do not show the early high threshold dip because short pulses *are not* able to stimulate sufficiently early in the cycle. The major or late dip however, can be revealed by all stimulus durations *from* 0 1 to 13 0 msec

Although innumerable workers have studied the relative refractory period of cardiac muscle they have failed to find or comment on these oscillations in the course of recovery for three significant reasons. In studies of one type stimuli of a fixed magnitude (usually some multiple of the threshold value) were employed this technique obviously would not reveal the dips. In other investigations although the stimulus strength was varied to determine thresholds *at different* intervals of the relative refractory period, the positioning of the test stimulus in the cycle was either at random, or at a selected interval after the R wave in undriven hearts where heart rate and duration of *refractoriness vary* (Sikand and Nahum, 1952) In either case the precise localization of oscillations lasting only 15 to 30 msec. would be unlikely Finally in many cases such short stimuli were employed that they failed to elicit any response during the

spread or conduction of the locally produced changes before the standard recording techniques detect the initiation of a response Confusion can be avoided if by irresponsive period is meant that interval during which a normal propagated response will not take place, but without implying that such a response will not eventually occur or that other reactions are not initiated Terms such as refractoriness and subnormality are likewise useful particularly when the precise meaning intended is indicated by qualifying statements

Even the term normal excitability is not very specific when subject to analysis "Normal" as employed here with application to the excitability of heart muscle implies the degree of excitability characteristic of the normal myocardium at rest All evidence indicates that excitability during diastole is a remarkably stable condition as shown, for example, by the constant level at which threshold values are maintained for long intervals in the same preparations In most instances a return to normal excitability following each beat is accomplished by attainment of the fully polarized state of the membrane Factors other than repolarization, however, may be involved in the recovery of normal excitability For example, in cooled hearts or portions thereof, the period of subnormal excitability following a contraction considerably outlasts the repolarization time In tissues such as nerve which show after potentials normal excitability is attained only after termination of the positive after potential It has not been established that there are after potenials in heart cells, this question will be given further consideration in Chapter V which deals with the cardiac cell, but it should be pointed out that in heart cells behaving as pacemakers there is no period during which the membrane potential is maintained at a constant level In these pacemakers the initial phases of the excitatory process appear to begin practically as soon as repolarization is completed It is not possible to identify or speak with assurance of normal excitability in such cases *Nevertheless, there* is a range of variability which can be considered normal and the concept of normal excitability should be retained

'DIP" PHENOMENA

It has already been pointed out that the recovery of normal excitability in the heart following a response is not a smoothly progressive process In strength interval curves obtained by means of stimuli of intermediate or long *duration*, fluctuations in the threshold are observed during the

ditions the dips have a fixed and predictable locus in the excitability recovery curve for stimuli of all durations and vary in a predictable manner if the entire curve is shifted by alterations of cycle length (Siebens et al 1951) Furthermore the position of the late dip is quite constant even when many different hearts are compared (Hoffman et al., 1955)

b) Dips can be shown by various types of stimuli high intensity induction shocks condenser and thyratron discharges and various durations of rectangular pulses

c) The fact that very short duration stimuli of relatively low intensity do not demonstrate dips is consistent with the idea that these fluctuations are a physiological phenomenon of recovery In any event such stimuli fail to excite except during diastole and the very latest phases of the refractory period

d) Occurrence of dips is not dependent on the use of a certain shape size form or type of electrode They have been revealed by platinum, chlorided silver saline wick, punctate, loop shaped (3 mm in diameter) bipolar and stigmatic monopolar electrodes and by electrodes making light contact with the surface or buried in the ventricular muscle wall (Orias et al 1950)

e) Dips are obtainable when testing the ventricular myocardium of hearts driven either through auricular electrodes or by natural S-A or A V nodal pacemakers This indicates that "dips" are not created by the driving pulse or by interactions between driving and testing stimuli

f) Dips are present in excitability curves obtained either from acutely exposed hearts or from closed chest preparations with chronically implanted electrodes (Pinkston et al. 1953) (see Chapter VII)

It may be added here that in experiments in which the standard arrangement of electrodes (see Chapter III) produced definite dips certain arrangements of electrodes created conditions unfavorable for their demonstration Even under these unfavorable circumstances however some flattening of the curves appeared in the dip areas. It is felt that this demonstration of possible unfavorable electrode placements does not negate the conclusion that fluctuations in thresholds for applied stimuli do characteristically occur during the relative refractory period (Orias et al 1950 see also Chapter V)

PHYSIOLOGICAL MEANING OF THE DIP PHENOMENON An analysis of the factors causing the observed dip in the curve depicting the time-course of the recovery of excitability presents many *difficulties*

part of the cycle where the dips are located On the other hand, it is interesting to note that if the data of certain other investigators are plotted with an interrupted line joining each threshold determination in place of the smoothed line employed, in many cases dips are revealed during the relative refractory period (turtle heart, Gilson, 1935, cat auricle, Eccles and Hoff, 1934, Burgen and Terroux, 1953) Furthermore, in speaking of responses to stimuli placed early in the cycle, Lewis and Master (1925) state that such a stimulus may yield a response while another placed only slightly later in the cycle may not, this would indicate that they too observed some fluctuation of the recovery of excitability to test shocks

When first recognized, it was thought that the "dips" might be artefacts resulting from some particular aspect of the testing techniques employed Consequently an extensive series of experiments was performed which allowed the following conclusions (Orias, et al, 1950)

TABLE 2—*Position of Dips in Ventricular Excitability Cycle*

Exp No	Cycle Length msec	Duration of Test Shock	End of Ab Ref Period (msec after Beat Origin)	Time and Duration of Dip after Origin of Cycle	
				Primary msec	Major msec
34	480	13	90	90 100	120-170
35	480	13	100	110-120	140-190
38	480	13	70	70-80	100-140
38	480	3	120		120-140
40	480	13	100	100-110	130 160
40	480	3	110	110-120	150-170
42	480	13	60	110-120	130-170
49	400	13	60	80 120	160-190
55	400	13	80	90-100	120 150
64	400	13	80	90 100	120-140
70	400	13	80	80 90	110-130
71	400	13	110	110 120	130-160
87	400	13	85	90-110	130 160
94	450	3	140		160 170
95	400	3	115		140 160
135	400	3	130	130-140	160 170

a) As shown in Table 2, the dips are present at specific intervals of the recovery period They are positioned with respect to the instant of initiation of the beat and the duration of the cycle Under uniform con

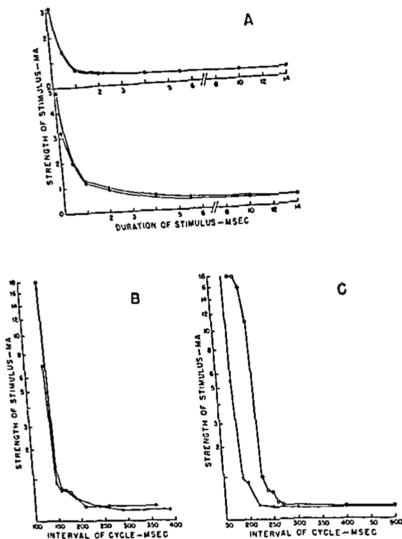


FIGURE 20 A—Strength-duration curves of auricle (top) and ventricle (bottom) obtained at same interval during diastole when the heart was artificially driven (x——x) and when beating spontaneously (o——o) B—Auricular and C—ventricular strength interval curves obtained when the heart was artificially driven (x——x) and undriven (o——o) Rate approximately constant throughout. Note slight effect of direct drive on duration of ventricular refractoriness.

because of the complexity of the tissue involved A strength interval curve showing an *early* and *late dip* and a phase of supernormality suggests the occurrence of a damped oscillatory process Spontaneous oscillations in membrane potential have been observed in many tissues (skeletal muscle, Adrian and Gelfan, 1933, nerve, Cole, 1941, smooth muscle, *Eccles and Magladery, 1937, Bozler, 1942-43*) and under a variety of conditions (polarization effects, Harris and Moe, 1942, Hodgkin, 1951, calcium lack, Brink, 1954, associated with tonus changes, Bozler, 1943) However, there is no evidence that the dips in the excitability curve are associated with any oscillatory changes in membrane potential of cardiac muscle (see Chapter V) Although the dips are associated with a change in sensitivity of the myocardium to anodal and cathodal current (see below), it is likely that other phenomena of the recovery process are related to their production At present there is no complete explanation of the underlying cause of these transient periods of enhanced excitability to stimuli applied during the relative refractory period However, some additional discussion of the dip phenomenon will be found in subsequent chapters dealing with the transmembrane potentials of cardiac muscle and with *vulnerability of the heart to repetitive firing* and fibrillation

METHODS OF STIMULATION AND VARIATIONS IN RESPONSE

The results reported here were obtained with a standard placement of driving and testing electrodes A set of three electrodes, a common anode separated from individual driving and testing cathodes by a distance of 5 7 mm, was applied to the base of the right ventricle when the ventricle was being driven directly A test anode and cathode alone were placed on the ventricle when the driving stimuli were applied to the auricle The strength duration and strength interval curves obtained were practically the same *in both cases, the only* consistent difference being a shorter absolute refractory period under direct drive (Figure 20 A and C) Similar results were obtained in the case of auricular muscle (Figure 20 A *and* B) *An additional series of experiments* was designed to determine to what degree electrode placements could influence the responses which have been described A single electrode, either anode *or* cathode, was placed *on the* surface of the ventricle The other electrode of the required pair was placed on the neck of the animal *In such cases the* excitability of the heart could be tested by means of a *localized* (stigmatic) anode *or* cathode paired with a *diffuse* cathode or anode, re

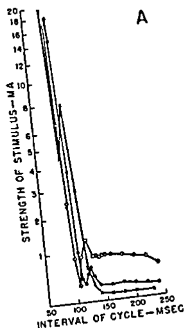
spectively This technique of monopolar stimulation yielded the following results

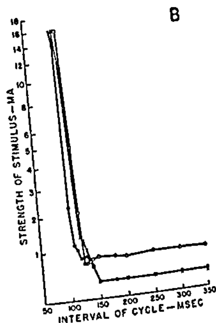
STIMULATION WITH A STIGMATIC CATHODE When excitability was studied by this technique the thresholds during dia tole were similar to those revealed by the usual bipolar stimulation However, as the test pulse was positioned progressively earlier in the relative refractory period, the threshold rose much more steeply than with bipolar electrodes and the late dip was either absent or revealed only at much higher stimulus intensities (Figure 21) Subsequently when the test pulse approached the border of the absolute refractory period the thresholds to "cathodal" stimulation again approximated those of the bipolar curve. The early dip when revealed by one technique of stimulation was also shown to be present at similar stimulus intensities by the other

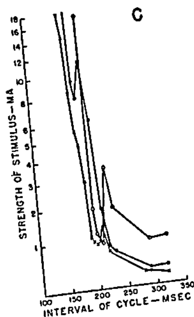
STIMULATION WITH A STIGMATIC ANODE Diastolic thresholds to "anodal" stimulation were uniformly much higher than bipolar or "cathodal values (Figure 21) When the stimulus was advanced earlier and earlier into the refractory period the 'anodal' thresholds rose very slowly during the late phases of refractoriness in most experiments Thresholds remained considerably below those of the "cathodal" stimulations but were quite similar to those obtained with bipolar electrodes. Early in the refractory period, however the anodal thresholds rose precipitously and usually exceeded the cathodal" and bipolar values at the same intervals Finally it was found that the late or major dip was often quite prominent in anodal" strength interval curves and sometimes the thresholds were actually lower than those of diastole "Anodal" stimulation revealed in certain experiments an actual supernormality during the refractory" period

INTERPRETATION OF RESULTS OF APPLICATION OF SUCH STIMULI The strength interval curve obtained with bipolar stimulation

during a portion of the relativ refractory period they are lower than those shown by either the cathodal or bipolar curves. C—Similar curves obtained from a different ventricle. Note that the bipolar curve (x——x) tends to follow the most effective portions of the anodal (o——o) and cathodal (•——•) curves. D—Bipolar curve on an expanded time scale with inserts showing the electrogram complexes obtained at various times and the position of the recording and testing electrodes on the ventricle. Complex 1 is that obtained when stimuli originate near the test cathode and 2 when near the anode. Initial downward deflection in each electrogram is the stimulus artefact.







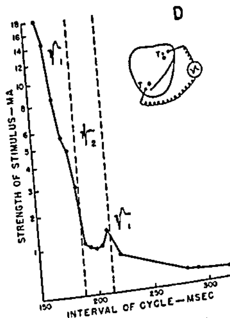


FIGURE 21 Strength interval curves obtained in A—ventricle and B—auricle with bipolar (●—●) anodal monopolar (o——o) and cathodal monopolar (x——x) stimuli Note that during late diastole thresholds to anodal stimuli are higher but

PHYSIOLOGICAL EXCITATION OF THE HEART In dealing with experiments on the excitability of the heart, the fact must always be kept in mind that all testing stimuli applied can hardly be considered physiological Although electrical stimuli are of the same nature as the intrinsic stimulating process, it would certainly be unsafe to conclude that all strengths of stimuli have the same ultimate effect on the heart. Very strong stimuli which reduce the absolute refractory period practically to zero and which may have an effect lasting through several cycles probably act by producing more than an easily reversed local modification of membrane polarization. But even if electrical stimuli of exogenous origin cannot be regarded as "physiologic" it is nevertheless true that the propagated reactions to such stimuli do constitute a physiological process The nature of the stimulus does not determine the nature of the response because propagation of excitation is an intrinsic process.

The actual strength of the intrinsic excitatory process in a pacemaker which initiates propagation of the action potential over the heart is not known. For nerve the strength of the propagating "stimulus" has been calculated to be of the order of three to ten times the normal threshold value (Bishop 1931 Hodgkin 1937) Similar calculations have not been made for the heart, although comparisons between strength of intrinsic and extrinsic stimuli have been attempted (Junkman 1925 Witz, 1938) These investigators showed that an impulse originating in the auricle will evoke contraction of a ventricle which has been *sufficiently* depressed by drugs to require a doubling or quadrupling of the strength of applied threshold stimuli At *any rate*, even if in the heart the stimulating value of intrinsic excitation were much higher than this it still would not be able to stimulate during the major portion of the period of subnormal excitability It can be concluded that for both intrinsic and extrinsic excitation, there is a *true* effective refractory period. That this is actually the case is shown by the familiar "compensatory pauses following extrasystoles. Both intrinsic and extrinsically applied stimuli are thought to act by initiating a localized depolarization which normally eventuates in a propagated change in membrane polarization Once this has occurred restimulation must await at least partial recovery of the normal polarized state (see Chapter V) Consequently after each beat the heart becomes first irresponsive and absolutely *refractory*, and then irresponsive and relatively refractory to all excitatory influences

(Figure 21 C and D) appears to be a composite of the most effective portions of the stigmatic anodal and cathodal curves Thus, during the interval of the late or major dip, activity should originate in the immediate vicinity of the anodal electrode but at certain other times, the cathode should be more effective Evidence of such a shift in the site of beat origin has been obtained

When one recording electrode was placed close to the cathode and the other close to the anode, the direction of the initial and major electrogram deflections was reversed when the test pulse was advanced from diastole into the terminal portions of the relative refractory period and reverted to the original configuration as the boundary of the absolute refractory period was approached (see Figure 21 D) Similarly, when *two pairs of bipolar recording electrodes were employed, one pair near* the test cathode and the other near the test anode, measurements of the time which elapsed between stimulation and arrival of propagated activity at each electrode pair revealed a definite shift in the site of impulse origin During diastole activity was first detected near the test cathode, during the major dip it began in the anodal surround, and early in the *relative refractory* period the cathodal surround was again the location from which propagation began This origin of the impulse near the anode rather than the cathode does not necessarily indicate an anodal "make" stimulation (Rosenblueth, 1941)

Stimulation on the 'break" of current flow is known to occur at the anode under many conditions and has been observed in studies of single myocardial fibers (Chapter V) Furthermore it is known that anodal current (current passing in across the membrane will *repolarize excit* able tissues (Pfluger, 1859, Kahn, 1941) Indeed, propagated repolarization resulting from anodal current pulses of adequate strength *has been known for many years (Biedermann, 1879)* and has recently been supported by Weidmann, (1951) on the basis of the most direct form of evidence It is thus quite likely that the apparent preferential stimulation at the anode during the relative refractory period occurs because during the flow of stimulus current repolarization under the anode is accelerated This repolarization lowers the threshold and as a result anodal break stimulation eventuates when the current flow ceases This mechanism may also explain the slightly shorter latencies which are present when the test pulse is applied at certain intervals of the cardiac cycle

PHYSIOLOGICAL EXCITATION OF THE HEART In dealing with experiments on the excitability of the heart, the fact must always be kept in mind that all testing stimuli applied can hardly be considered physiological Although electrical stimuli are of the same nature as the intrinsic stimulating process it would certainly be unsafe to conclude that all strengths of stimuli have the same ultimate effect on the heart. Very strong stimuli which reduce the absolute refractory period practically to zero and which may have an effect lasting through several cycles probably act by producing more than an easily reversed local modification of membrane polarization But even if electrical stimuli of exogenous origin cannot be regarded as "physiologic" it is nevertheless true that the propagated reactions to such stimuli do constitute a physiological process The nature of the stimulus does not determine the nature of the response because propagation of excitation is an intrinsic process.

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EXCITABILITY CYCLE AND ELECTRICAL EVENTS OF THE CARDIAC CYCLE

A summary of the temporal relationship between the excitability changes and the electrical activity of the heart can be presented at this time If the electrical events as portrayed by the local bipolar electrogram are considered, the usual sequence of occurrences is as follows *Concurrently* with the inscription of the R wave, heart muscle becomes refractory to stimulation Just prior to the beginning of the T wave of the local electrogram, the cardiac muscle again becomes excitable by reasonably strong stimuli Subsequently, the recovery of excitability increases rapidly, the first dip occurs, fast recovery continues until the recession following the late or major dip, and then recovery proceeds more slowly until the resting level is attained coincident with completion of the T deflection The irresponsive period is co extensive with the total period of subnormal excitability (Burdon Sanderson, 1879) A phase of slight "supernormality" is present in some hearts immediately after the inscription of the T wave of the cardiac electrogram The temporal correlation between these events and the standard electrocardiogram depends, of course, on the area of ventricular myocardium studied

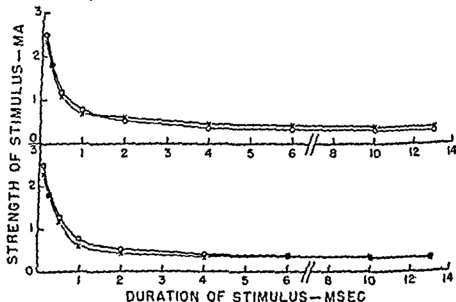


FIGURE 22 Similarity of strength-duration curves (excitability) of auricle (x——x) and ventricle (o——o) when the same electrodes are employed to test both chambers in the same heart. An hour elapsed between taking of upper and lower curves

EXCITABILITY CYCLE OF THE AURICLE

When the excitability of the mammalian auricle is tested by accurately timed stimuli of controllable shape, duration and intensity, essentially the same changes are found as have been described for the ventricle (Brooks et al, 1950) When the level of resting excitability in the auricle and ventricle of the same heart are compared by means of the *same testing electrodes* the strength-duration curves of both chambers are found to be approximately superimposable (Figure 22) Strength interval curves depicting the time course of the recovery of excitability in auricle and ventricle of a single heart uniformly reveal a somewhat longer absolute and total refractory period in the latter chamber (see Figure 16) The auricular curve shows the same irregularities or dips as have been described for the ventricle, and although they occupy the same position in time during the relative refractory period they tend to be somewhat shallower and shorter in duration As is the case in the ventricle, the terminal boundary of the absolute refractory period is dependent on the duration and strength of the test pulse employed

There is an irresponsive period during the recovery of auricular excitability in terms of the initiation of a normally propagated impulse just as has been described for ventricular muscle (Figure 18) When excitability is tested by means of stigmatic anodal or cathodal electrodes the results are again similar to those described for the ventricle both a period of enhanced susceptibility to anodal shocks and the initiation of activity in the area of the anodal electrode are found (Figure 21) at certain intervals of the cycle. The effect of driving stimuli is of little importance in determining either the magnitude of the diastolic threshold to stimuli of various durations (Figure 20) or the overall configuration of the auricular strength interval curve. A post refractory period of slight supernormality (Figure 17) is observed more frequently in the auricle than in the ventricle (Brooks et al. 1950)

All results obtained from acute preparations have been reproduced in dogs with chronically implanted electrodes (Pinkston et al 1953) (see Chapter VII) this finding is in disagreement with the results of some workers (Sikand and Nahum 1952) Reasons for the discrepancies noted have been discussed in Chapter III and in an earlier section of the present chapter An additional factor will be mentioned at this time In the investigation of the time-course of recovery in auricular muscle the exact limits of the absolute refractory period for stimuli of limited strength

EXCITABILITY CYCLE AND ELECTRICAL EVENTS OF THE CARDIAC CYCLE

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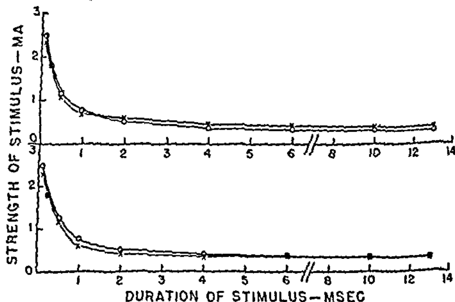


FIGURE 22 Similarity of strength-duration curves (excitability) of auricle (x——x) and ventricle (o——o) when the same electrodes are employed to test both chambers in the same heart. An hour elapsed between taking of upper and lower curves.

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are not easily determined, for even short duration stimuli above a certain strength give no response at all, a "nothing phenomenon" (Orias, et al, 1950, see Chapter VI) throughout a considerable proportion of the relative refractory period Very early in the cycle thresholds for extra systoles and this "nothing phenomenon" are quite close together and small increments of shock must be employed to avoid jumping from a subthreshold intensity to a strength above that which will produce an extrasystole Because of this complicating factor, the accurate delineation of the course of recovery in auricular muscle can be accomplished only if the various parameters of the test situation are held under the most rigid control

SUMMARY

Modern electrophysiological techniques were employed in studies of the excitability of the mammalian auricle and ventricle Older concepts of *the cyclical occurring changes in excitability were amplified*, new phenomena of considerable importance were discovered and described Among other things, a more adequate picture of the phases of refractoriness, the relationship between latency and the irresponsive period, and the location and extent of the vulnerable period was provided The electrical events of the cycle were related to the observed changes in excitability

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of depolarization of all fibers Similarly a decrease in magnitude will also result from the return to activity of some of the fibers in the depolarized area under the inactive electrode. Furthermore changes in conduction velocity will give rise to changes in the duration of the monophasic potential, even though there may have been no change in the duration of activity in any given area of membrane. Finally, since the magnitude of the monophasic action potential depends directly on the degree of shunting in the external medium, the exact determination of the amplitude of the resting and active membrane potential is difficult if not impossible

The need for an accurate technique for measuring the normal membrane potential in heart cells and the time course of depolarization and repolarization of heart muscle was met by the methods and experimental procedures devised by Coraboeuf and Weidmann (1949), Draper and Weidmann (1951) and Woodbury et al. (1951) Their studies demonstrated that the potential difference *across* a limited area of muscle membrane of a single heart fiber could be faithfully recorded by use of an intracellular microelectrode of the type developed by Ling and Gerard (1949) By means of this technique the exact time course of depolarization and repolarization could be recorded and accurate measurements of the resting and active membrane potential could be made Information thus obtained concerning the state of polarization of the muscle membrane serves as a better basis for correlation with studies of excitability and refractoriness than the less direct and more variable measurements obtained with surface electrodes

DIRECT RECORDING

MICROPUNCTURE TECHNIQUE Early studies of the transmembrane potentials of excitable tissues performed on the giant axon of the squid by Curtis and Cole (1940 1942) Hodgkin and Huxley (1939 1945) and Hodgkin Huxley and Katz (1952), revealed many of the properties of excitable membranes and provided a theoretical explanation for the observed resting and action potentials of nerve The application of a similar technique to other tissues was made possible by the development of the glass capillary microelectrode by Ling and Gerard A fine glass capillary, measuring one micron or less at the tip and filled with isotonic KCl was inserted into a single fiber of the frog sartorius muscle and the potential difference across the resting membrane was determined under various conditions. Nastuk and Hodgkin (1950) subsequently refined these

V The Heart Cell–Transmembrane Potentials of Cardiac Muscle

This is a presentation of new facts about the basic processes involved in the reactions of the ultimate unit of cardiac activity, the cardiac cell and its membrane This information, obtained chiefly with the new technique of intracellular recording, represents the results of studies on the most basic processes of heart function

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INDIRECT RECORDING

THE DEMARCATION OR INJURY POTENTIAL The monophasic action potential of the heart, recorded with one electrode on injured or depolarized and supposedly inactive tissue and the other electrode on active normal muscle, has been employed for many years to reveal the time course of depolarization and repolarization of muscle membrane (Biedermann, 1895, Burdon Sanderson, 1879) The monophasic action potential is, of course, the change produced in the existing potential difference recorded between depolarized and normal tissues when a wave of activity depolarizes and even momentarily reverses the polarity of the normal membrane In other words the constantly present injury or demarcation potential is a measurement of the membrane potential of normal heart muscle cells and the monophasic action potential reveals the changes in this potential which occur during activity Measurement of the monophasic action potential has been employed to correlate changes in the state of the membrane with observed variations in excitability and with the simultaneous cardiac electrogram or myogram Numerous references to studies of this type are cited by Schutz (1936) and Lepeschkin (1951) Admittedly, however, use of the monophasic action potential has numerous disadvantages and is at best a record of the average time course of the membrane potential changes in many cells (Churney *et al*, *1948*) For example, to consider first the muscle under the active electrode, a decrease in the magnitude of the monophasic action potential will result from either, 1) a decrease in the total number of fibers depolarized by a given stimulus, 2) an alteration in the sequential change in membrane polarity of the fibers in this area, or 3) a decrease in the degree

The possibility that penetration of a fiber by the tip of the microelectrode might injure the membrane and thus distort the true resting potential seems unlikely in view of the experiments of Nastuk and Hodgkin (1950) and Draper and Weidmann (1951) These investigators found that when the resting potential of a given fiber was measured by one intracellular electrode, the insertion of another electrode into the same fiber at a distance of only two hundred microns produced little if any change in the recorded potential Similarly, alteration of the resting potential by a liquid junction potential between the 3 M KCl in the microelectrode and the myoplasm of the fiber is unlikely on both theoretical and experimental grounds (Nastuk and Hodgkin 1950 Draper and Weidmann 1951) Thus the technique described accurately measures the resting membrane potential of excitable cells Some slight distortion of the upstroke of the action potential will occur if the time constant of the recording apparatus is long, however at most this effect will produce only slight modifications in the magnitude and shape of the overshoot the slow change in potential during repolarization will be recorded faithfully In summary then it can be said that use of an intracellular microelectrode gives a true picture of the time course of depolarization and repolarization in a single cardiac muscle fiber and in addition provides a remarkably accurate measurement of the magnitude of transmembrane potentials

VENTRICULAR TRANSMEMBRANE POTENTIALS The normal transmembrane potentials of a single fiber of the spontaneously beating dog ventricle recorded in situ in the open chest preparation are similar in shape to the monophasic injury potential of the same tissue (Schütz, 1936 H C and C J Wiggers, 1935) A typical record of the action potential of a single ventricular fiber is seen in Figure 24-A It shows a constant resting potential during diastole an abrupt phase of depolarization that terminates in a peaked reversal of membrane polarity a plateau of long duration during which the membrane potential is close to zero and a final phase of slow repolarization The rising phase of the action potential of a single ventricular fiber of the dog's heart lasts 1 2 msec., the reversal 6-15 msec and the phase of repolarization 100-150 msec The duration of the plateau varies with heart rate (see Chapter VIII) but normally lasts approximately 100 msec. The magnitude of the resting potential and reversal measured from carefully selected records (Hoffman and Suckling 1952 a) amounts to 80-90 and 10-20 mv respectively Since all possible recording artifacts tend to decrease the magnitude of

methods and used an electrode filled with 3 M KCl to minimize the junction potential between electrode and myoplasm The same technique was successfully applied to the ventricle of the frog heart by Woodbury et al. (1951) and to the isolated false tendon of the dog and kid heart by Draper and Weidmann (1951)

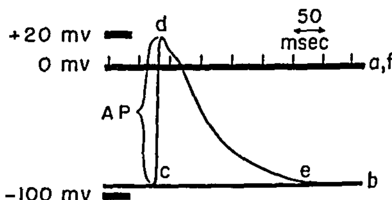


FIGURE 23 Diagrammatic representation of a transmembrane action potential (c d e) from a single fiber of the dog auricle Resting potential (b) and a zero potential line a f

In practice, the measurement of the transmembrane potential is accomplished in the following manner When both the microelectrode and the indifferent electrode are extracellular in position, no potential difference is recorded (Fig 23, line a) However, when the tip of the microelectrode pierces the membrane of a single fiber a sudden potential of 80 90 mv is recorded with the inside of the fiber negative to the indifferent electrode, (Fig 23 line b) This potential difference across the muscle membrane is called the resting potential and remains at the same value as long as the tissue is quiescent Following stimulation, however, there is a rapid change in the membrane potential of such a nature that the intracellular microelectrode momentarily becomes positive with respect to the indifferent electrode (Fig 23, line c d) Thus at the peak of the action potential the membrane is not only depolarized but actually exhibits a reversal of polarity or overshoot amounting to 15 30 mv Immediately after this reversal, repolarization of the membrane commences and the resting potential is restored (Fig 23 line d-e) If the microelectrode is then withdrawn from the fiber the trace returns to the original line of zero potential (Fig 23, line f)

Certain minor variations in the time course of the action potential are demonstrated at times by certain hearts Some preparations show a shallow dip between the spike and the beginning of the plateau the plateau it self may be curved or flat, and lie slightly above or below the line of zero potential. In addition some fibers demonstrate a slow loss of membrane potential during diastole that seemingly is not the result of injury since subsequent cycles giving the same initial resting potential, show the same slow depolarization preceding the upstroke of the action potential. This slow diastolic depolarization is probably related to pacemaker activity discussed subsequently

The temporal relationship between the action potential of a single fiber and the local ventricular electrogram of the intact in situ heart is seen in Figure 24-C The upstroke of the action potential coincides as expected, with the R wave of the electrogram the plateau with the RT segment, and the phase of repolarization with the T wave

The transmembrane potentials of single fibers of the isolated papillary muscle of the dog's right ventricle are in all respects similar to those obtained from the surface cells of the intact heart (Hoffman and Suckling 1953a) Figure 24-D E, F demonstrates typical records and their tem poral relationship to the simultaneous unipolar electrogram The average values for the resting potential and action potential of single fibers of the papillary muscle are 85 90 mv and 105 115 mv respectively This prepara tion therefore may be employed as a representative indicator of the behavior of ventricular muscle in general and offers several advantages over the intact heart for many types of experiments

AURICULAR TRANSMEMBRANE POTENTIALS The normal trans-membrane potentials recorded from single fibers of the intact auricle by means of an intracellular microelectrode are shown in Figure 25 In many respects they resemble action potentials of ventricular muscle fibers and demonstrate a constant resting membrane potential during diastole of 80-90 mv and a rapid depolarization on excitation resulting in a membrane reversal of 10-20 mv Following this depolarization however, the auricular records show an immediate slow phase of repolarization without the intervening plateau typical of ventricular muscle (Hoffman and Suckling 1952a) The shape of the repolarization limb of the auricular action potential varies in different hearts and may be almost straight or show some upward or downward convexity (Fig 25 A, B) This varia tion seems to depend primarily on the level of tonic vagal activity (Hoff

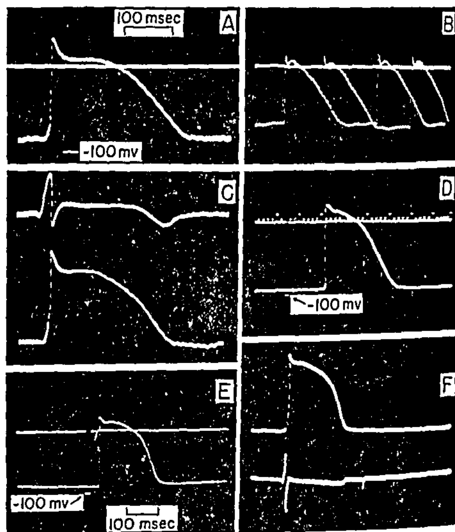


FIGURE 24 Ventricular transmembrane action potentials and electrograms See text for descriptions A B C—recorded from cells in situ D E F—from isolated papillary muscles Time marks in D represent 10 and 50 msec. intervals (Retouched to show action potential upstrokes by dotted lines)

recorded potential (i e, injury, movement, etc) these values are probably somewhat low In any heart the membrane potential records obtained from many different fibers are remarkably constant with respect to amplitude, shape and duration As seen in Figure 24-B, many cycles of spontaneous or induced activity can be recorded from a single fiber without any change or distortion in the form or amplitude of the action potential.

fiber and time course of membrane potential Just as in the case of the ventricular fiber many cycles of spontaneous or evoked activity can be recorded without any appreciable change in the configuration of the action potential (Fig 25 C)

The transmembrane potentials of single fibers of isolated preparations of either right or left atrium or auricular appendage are both qualitatively and quantitatively similar to those recorded from fibers in the intact heart. The magnitude of the average resting and action potentials is 85 90 and 105-110 mv respectively and the duration of the action potential is usually the same at equivalent rates in either the intact or isolated preparation (Fig 25-D E)

The relationship of the action potential of a single fiber of the isolated auricle to the local unipolar electrogram is shown in Figure 25 F (Hoffman and Suckling 1952b) As in the case of ventricular muscle, the depolarization of the membrane coincides with the R wave of the electrogram and its repolarization with the T_a wave The repolarization of auricular muscle commencing as it does immediately after the end of depolarization explains why only a small T wave is normally recorded from mammalian auricle.

Studies of the transmembrane potentials of the cat auricle (Burgen and Terroux 1953a) have given results qualitatively similar to those obtained from the dog heart. However the magnitude of the resting and action potential reported for the cat is on the average 60 4 and 65.2 mv respectively Since the absolute value of the transmembrane potential varies greatly in different tissues (see Table I Chapter II), this difference between dog and cat auricle is not surprising However several known factors may have contributed to the apparent discrepancy In the first place the Tyrode solution employed for cat auricle contained more K (5 6 mM) and less Ca^{++} (1 9 mM) than was used for the dog heart. Secondly the smaller average diameter of cat auricular fibers makes penetration without injury much more difficult (Trautwein and Zink, 1952) Finally a low resting potential will of necessity decrease the magnitude of the action potential because of the known effect of membrane potential on sodium current (Weidmann 1955a see discussion below)

TRANSMEMBRANE POTENTIALS OF SPECIALIZED TISSUES Of the three specialized tissues in the mammalian heart—the sino-atrial node

man and Suckling, 1953a) and to a lesser degree on the extracellular concentrations of Ca^{++} and K^{+} (Hoffman and Suckling 1953b) Although in a given heart some difference in shape of the action potential may be recorded when different areas of the auricle and atrium are explored, there appears to be no consistent relationship between location of the

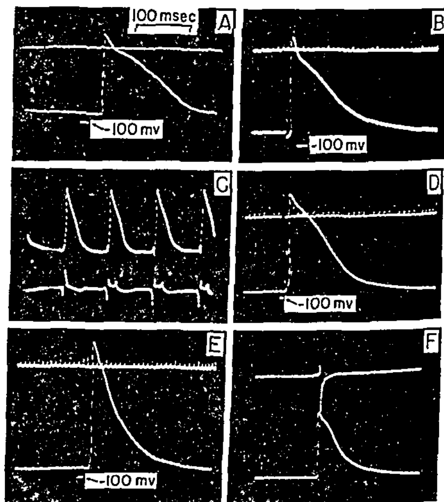


FIGURE 25 Auricular transmembrane action potentials See text for descriptions *A B C—recorded from cells in situ D E F—from cells in isolated portions of* auricular tissue Time scale in B D and E shows 10 and 50 msec. intervals Unipolar electrogram in bottom trace of C and top trace of F (Retouched to show action potential upstrokes by dotted lines)

been employed by many investigators following the initial studies of Coraboeuf and Weidmann (1949) and Draper and Weidmann (1951) To date the largest part of the available information concerning the membrane behavior of cardiac muscle has been obtained from this preparation (Weidmann 1951 1952, 1955a b Trautwein et al., 1952 1954a, b Coraboeuf et al. 1953a, b 1954) Indeed Purkinje fibers are almost ideally suited to microelectrode studies because of their large diameter and minimal contractility, both of these factors favoring successful impalement without danger of either injury to the fiber or displacement of the electrode tip

The resting transmembrane potential recorded from a single fiber of the dog s Purkinje system amounts to 90±6 mv and the action potential 121±5 mv (Draper and Weidmann 1951) Values somewhat higher than these are found in the false tendon of ungulates (resting potential = 98 mv., action potential = 132 mv Weidmann 1955b) The time course of the transmembrane action potential of the dog Purkinje fiber is shown in Figure 26A, B) The maximum upstroke velocity is 510±140 volts/sec. (Draper and Weidmann 1951) and the spiked reversal of membrane polarity at the peak of the action potential is not only larger but also of shorter duration than in ventricular or auricular fibers Furthermore the duration of the plateau is considerably longer at equivalent rates than that of plain ventricular muscle (Trautwein et al 1954) Another difference between the Purkinje fiber and non-specialized cardiac muscle is the time course of the membrane potential during diastole As seen in Figure 26C, D many Purkinje fibers reveal a slow loss of resting potential during diastole the highest value of resting potential is thus attained immediately after repolarization and subsequently the membrane potential falls slowly until the next action potential occurs This slow diastolic depolarization is discussed below under Pacemaker Activity"

The electrical properties of the Purkinje fiber have also been studied by inserting two microelectrodes into the same cell leading in current through one electrode and recording potential by means of the other (Weidmann 1951 1952) The values thus obtained for the passive electrical properties of the membrane are compared with similar values in nerve and muscle in Table 3 It is of interest at this time to note that a large drop in membrane resistance has been recorded in this tissue during the upstroke of the action potential, as is the case in nerve and skeletal muscle. However unlike these two tissues, in the Purkinje fiber

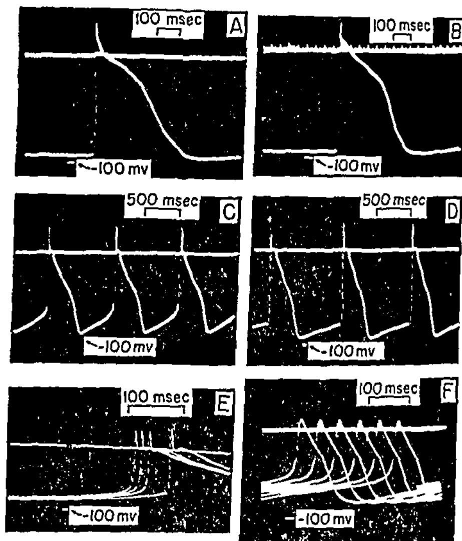


FIGURE 26 Transmembrane action potentials of single Purkinje fibers A and B show *induced activity in quiescent preparations* Spontaneous activity *recorded from a* pacemaker area (C) and from a closely adjacent area (D) E shows records obtained from a fixed locus in the Purkinje fiber when activity arises at that locus and when due to pacemaker shift, the activity is propagated to the recording *site* F *shows pacemaker activity from an auricular fiber (Retouched to show action* potential upstrokes by dotted lines)

the atrio ventricular node and the ventricular conducting system—only the latter has been studied extensively by microelectrode techniques Single Purkinje fibers in the false tendons of dog sheep, and kid hearts have

of the membrane In the case of mammalian tissue at 38° C. the expression for the resting potential can be simplified to

$$\text{Resting Potential} = 61.5 \log_{10} \frac{[K]_i}{[K]_o}$$

If the approximate K^+ connencentration of cardiac muscle is between 130 and 150 mM intracellular water (Lowry 1943 Robertson and Dunihue 1954) and the concentration of K^+ in Tyrode solution is 2.7 mM/l then the resting potential hould be about 105 mv Obviously the experimental values closely approximate that predicted by the theory and the slight departures noted may quite possibly be explained by the contributions of other ions to the transmembrane potential

Stronger evidence for the dependence of the resting potential on the potassium concentration gradient is afforded by the demon tration that, within limits the resting potential varies as a linear function of the log of the outside K concentration (Burgen and Terroux 1953a b) and is largely uninfluenced by changes in the extracellular sodium concentration (Draper and Weidmann 1951) Experimental data thus strongly indicate that the resting transmembrane potential of cardiac *muscle results* primarily from the partition of K^+ ions by the fiber membrane

ACTION POTENTIAL It is also assumed that the upstroke of the action potential results from a change in membrane resistance permitting a sudden rapid inward sodium current (see Chapter II) The demonstration in monophasic action potentials of the turtle heart (Cranefield et al 1951b) and in Purkinje fibers (Draper and Weidmann 1951) that both the magnitude of the reversal and the maximum rate of rise of the action potential vary as predicted (Hodgkin and Huxley 1952a) when the extracellular sodium concentration is decreased indicates that the mechanism of depolarization in cardiac muscle is not different from that in other excitable tissues

REPOLARIZATION Repolarization of nerve seemingly results from a decreased inward sodium current (due to decreased permeability to Na or to "inactivation Chapter II) and a rise in potassium permeability and outward potassium *current. In* cardiac muscle however the nature of the repolarization process remains uncertain Studies of the effect of transmembrane potential on sodium permeability (Weidmann, 1955a) strongly suggest that the descending limb of the initial spike or reversal results from a decrease in inward sodium *current.* The processes re

TABLE 3—*Electrical Constants of Excitable Tissues*

Tissue	Fiber Diameter	Membrane Potential	Length Constant	Membrane Resistance	Membrane Capacity	Time Constant	Internal Resistance
Units	μ	mV	cm	Ωcm²	μF-cm⁻²	msec	Ωcm
Squid Axon	500	61	0.25	700	1.5	1 0	30
Sepia Axon	200	62	0 6	12 000	1 1	13 0	40
Carcinus Axon	30	82	0.2	6 700	1 35	9 0	60
Frog Muscle (Sartorius)	135	86	0.24	4 100	8 0	34 0	250
Purkinje Fibers	75	90	1 9	1 900	12 4	19.5	105

Data obtained from Eccles 1952 and Weidmann 1952

the transmembrane resistance returns to a high value immediately after the spiked reversal and increases progressively all during the plateau (Cranefield et al, 1951a, Weidmann, 1951) Furthermore, during the phase of repolarization no appreciable change in resistance has been recorded

IONIC BASIS OF CARDIAC TRANSMEMBRANE POTENTIALS

The nature of excitability and of potential changes during activity has been discussed at some length in Chapter II however, some consideration of the applicability to cardiac muscle of the theories mentioned seems pertinent

RESTING POTENTIAL The ionic theory of electrical activity (Hodgkin, 1951) postulates that the value of the resting potential, E, should be approximated by the expression for a potassium concentration cell

$$E = \frac{RT}{F} \log \frac{[K]_i}{[K]_o}$$

where K_i and K_o are the concentrations of potassium inside and outside the fiber respectively In addition, it must be assumed that the permeability of the fiber to other ions is low, and that the activity coefficients for potassium correspond to the concentrations and are equal on both sides

across the membrane of a single fiber during diastole. Equal increments of current gave rise to progressively greater depolarizations until the transmembrane potential was lowered to a critical level (the 'threshold potential") and a regenerative depolarization culminating in production of the action potential resulted The magnitude of this critical threshold

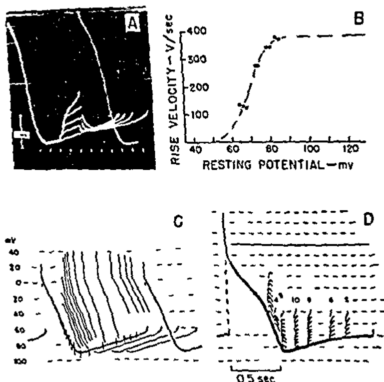


FIGURE 27 A. Subthreshold responses and the origin of a propagated response in a single Purkinje fiber

B Relationship between rising velocity of the action potential and the level of the resting potential as determined by the voltage-clamp technique.

C. Responses to stimulation during repolarization and subsequent slow depolarization of a single Purkinje fiber

D Determination of "threshold potential" in a Purkinje fiber at various intervals following activity Numbers indicate current strength required to elicit a propagated response at each interval. Note relative ease of stimulation during latter phase of repolarization and late in diastole. Compare with figure 28. (All figures from Weidmann J Physiol., 1951 1955)

sponsible for the plateau and subsequent repolarization, however, can be discussed only in terms of possibilities

The high membrane resistance recorded during the plateau suggests that the permeability of the membrane to both Na^+ and K^+ is low at this time Thus the unchanging membrane potential is not surprising However, even though tracer studies have shown that activity in cardiac muscle is associated with a periodic outflux of K^+ from within the fiber (Wilde and O'Brien, 1953), it has not been possible to relate this event, in time, to the phase of repolarization Furthermore, as mentioned previously, studies of membrane resistance do not provide any evidence of a rise in conductance during the repolarization limb of the action potential

Even though it is possible that repolarization of cardiac muscle does result from an outward potassium current, as is the case in nerve, conclusive data supporting this concept are not available Certainly the unique time course of recovery in cardiac muscle suggests that additional if not completely different mechanisms must be operative All that can be said at this time is that any change or series of changes resulting in a net outward current of positive ions would produce the observed restoration of membrane potential

SUBTHRESHOLD RESPONSES AND THE THRESHOLD POTENTIAL The voltage clamp studies discussed in Chapter II have shown that the permeability of a membrane to sodium ions is a function of the level of the transmembrane potential (Hodgkin and Huxley, 1952b) This relationship can be described in rather general terms as follows If the membrane potential is decreased from its normal value, sodium permeability rises and the inward sodium current increases This transfer of positive charge inward across the membrane produces an additional decrease in membrane potential and therefore a further augmentation of the sodium current However, a lower membrane potential also results in a larger than normal outward potassium current which tends to repolarize the membrane The threshold for a propagated action potential is the level of membrane potential at which the tendency to depolarize is greater than the tendency to repolarize

The concept of a threshold potential can be better understood by a consideration of the subthreshold responses of a single Purkinje fiber shown in Figure 27 A (Weidmann, 1951) In the experiment demonstrated, long lasting rectangular pulses of cathodal current were applied

depolarization the action potential began Similar evidence of slow depolarization in pacemaker areas of the false tendon of the dog ventricle has subsequently been recorded by other investigators (Trautwein 1953 Coraboeuf and Boistel, 1953 Hoffman and Suckling 1956)

A typical action potential recorded from a pacemaker region of an isolated Purkinje fiber is shown in Figure 26-C In addition to the slow depolarization mentioned above, such an action potential is distinguished by a slow upward curvature preceding the rapid upstroke and also by a decrease in magnitude of the peak reversal of membrane polarity (Fig 26-E see also Weidmann 1955b Hoffman and Suckling 1956) The differences mentioned can be fully appreciated when the pacemaker potential is compared with activity recorded from the identical area of the fiber during activity induced by a distant pacemaker (Fig 26-D, E)

The major determinants of the rate at which a pacemaker fires can now be discussed These are (1) the rate at which the transmembrane potential is lost, expressed by the slope of the slow diastolic depolarization and (2) the level of instability or threshold potential at which regenerative activity ensues Thus a decrease in temperature slows spontaneous activity by altering the slope of depolarization (Coraboeuf and Weidmann, 1954 Trautwein 1953) while changes in the concentration of extracellular Ca^{++} produce variations in the threshold potential (Weidmann 1955b) Other possibilities of course exist, such as a decrease in the level of resting potential attained immediately after repolarization additional discussion of such phenomena will be found in subsequent sections

The assumption can be made that normal pacemaker activity in both the S-A and A V nodal tissue of mammalian hearts is similar to that demonstrated in Purkinje fibers Although records from these specialized tissues are not available typical pacemaker activity has been recorded from dog auricular fibers under certain conditions (Fig 26-F) Also records from the sinus venosus of the frog and turtle heart reveal pacemaker activity resulting from slow diastolic depolarization like that observed in fibers of the mammalian Purkinje system (Brady and Hecht, 1954, Hutter and Trautwein, 1955) Furthermore the presence of a similar mechanism in normal, undifferentiated cardiac muscle is likely (Woodbury et al. 1951 Hoffman and Suckling 1952a) However the existence of other mechanisms of pacemaker activity under abnormal conditions and in ectopic foci such as have been postulated (Scherf and Terranova 1949 Prinzmetal et al. 1952) still remains a distinct possibility

potential in Purkinje fibers is approximately 65-75 mv inside negative (Weidmann, 1955b). The threshold potential might be called the level of membrane instability. This level at which a regenerative process will begin can vary. It is really an expression of the forces tending to maintain membrane polarization rather than a quantitation of forces tending to break it down.

SPONTANEOUS RHYTHMICITY

The nature of spontaneous rhythmicity in cardiac muscle has for many years been subject to only indirect investigation. Although the rate and regularity of spontaneous impulse formation had been determined and the presence of single or multiple pacemakers postulated (Rijlant, 1932; Eccles and Hoff, 1934), the underlying nature of the intrinsic excitatory mechanism remained uncertain. That this process was not inseparable from the property of refractoriness was apparent from the following observation. Cardiac muscle normally fails to beat until some time after full excitability has been restored. Attempts to record some indication of the nature of the processes operating in pacemaker areas revealed two major and somewhat similar types of activity. In some cases oscillatory changes in potential were recorded (Bozler, 1942-43). In others, slowly rising potentials initiated a propagated response after attaining a certain magnitude (Rijlant, 1932; Bozler, 1943). These results suggested that some smooth or oscillatory collapse of the normal polarization of pacemaker tissue fires a propagated action potential when a certain level of depolarization has been attained.

A direct demonstration of the membrane potential changes in pacemaker tissues was recently provided by the microelectrode studies of Draper and Weidmann (1951) performed on the isolated Purkinje fibers of the dog ventricle. This work revealed a constant difference between the transmembrane potentials recorded from pacemaker areas and those recorded from areas driven by the pacemaker. In the latter case, the resting membrane potential remained at a constant value until the area of membrane under investigation was abruptly depolarized by a propagated action potential. When the recording was obtained from a pacemaker area, on the other hand, the resting potential began to decrease immediately after the end of the repolarization and continued to fall until the level of instability was reached ("threshold potential") at which time a more rapid

required to attain this particular potential a change in the threshold current requirement may result from several different factors These will be discussed briefly

a) Changes in resting potential If the resting potential is 90 mv and the threshold potential is 65 mv., then a stimulus current sufficient to lower the membrane potential by 25 mv must be applied in order to stimulate. If on the other hand, the resting potential is only 80 mv., the stimulus must produce a drop in potential of only 15 mv to reach the threshold potential This relationship (shown in Fig 23A, B) can be stated in general terms as follows at resting potentials greater than the threshold potential, for a given value of membrane resistance the current required to stimulate is directly related to the resting potential Thus higher resting potentials result in an increase and lower resting potentials in a decrease of threshold current requirement. This relationship has been studied in detail by other investigators (Jenerick and Gerard 1953)

b) Changes in threshold potential It is quite obvious that any change in the magnitude of the threshold potential will change the threshold current requirement by the mechanism discussed above A higher threshold potential, therefore, is associated with an increase in excitability and vice versa (Fig 23-A)

c) Other changes There are obviously a number of other variables which will influence the threshold of an excitable tissue Among these membrane resistance is of paramount importance especially in cases when the stimulus duration is long Also important are the uncertain factors which control the relationship between potential and membrane permeability (see Chapter II) An understanding of the interrelationship between resting potential, threshold, and threshold potential is of considerable value in considering the changes in excitability that take place during repolarization of the excitable membrane.

THE NATURE OF REFRACTORINESS The discussion of the refractory periods of the mammalian ventricle in the preceding chapter has indicated that the recovery of excitability following activity is a complex process perhaps even more so than is the similar case in nerve or skeletal muscle Although little is known of the basic mechanisms which are ultimately responsible for the phenomenon of refractoriness such as physical and chemical changes in the membrane the changes in excitability observed during the refractory period can be partly explained by a consideration of the relationship between membrane potential and sodium current.

TRANSMEMBRANE POTENTIALS AND EXCITABILITY

Study of the relationship between the transmembrane potential and excitability is an interesting extension of the work summarized in the preceding chapter A series of investigations of this type, based on the recording of monophasic action potentials, has been summarized by Schutz (1936) The use of an intracellular microelectrode to directly record the transmembrane potential of a single fiber, however, provides a more refined and direct indication of the changes in potential that take place across a limited area of membrane Results obtained with this technique, therefore, are subject to more accurate interpretation than would otherwise be possible

CHANGES IN THRESHOLD As has been stated previously, the threshold potential of a myocardial fiber is that value of the transmembrane potential at which a regenerative depolarization takes place If, as is customary, the "threshold" of a tissue is measured in terms of current

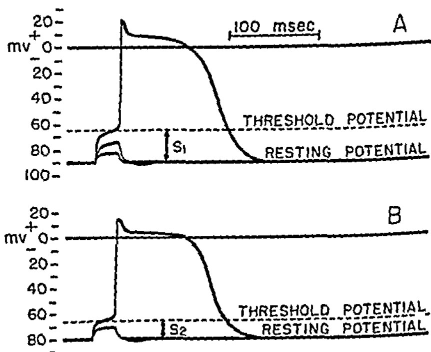


FIGURE 28 Diagrammatic representation of the changes in threshold of ventricular cells to applied stimuli resulting from changes in resting potential. S_1 and S_2 represent the magnitudes of the threshold stimuli.

as follows Under resting conditions, the stimulus intensity just adequate to give rise to a propagated response is one which depolarizes the fiber membrane to a critical level. This level, termed the level of instability or threshold potential is the transmembrane potential at which the resulting inward sodium current is adequate to complete depolarization. During recovery from activity however the threshold potential at which an adequate sodium current will eventuate is markedly changed and therefore the stimulus required to reach the critical or threshold potential is greatly increased

TEMPORAL RELATIONSHIPS BETWEEN MEMBRANE POTENTIALS AND EXCITABILITY When the excitability of ventricular muscle is studied by determining the stimulus intensity required to elicit a propagated response during and after the repolarization process of a single fiber it is found that the absolute refractory period lasts from the onset of activity until repolarization is approximately half completed (Fig 29)

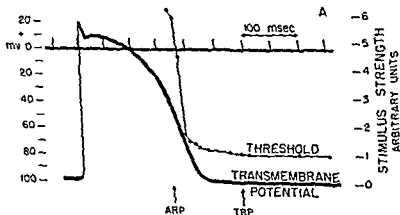


FIGURE 29 Relationship between transmembrane potentials and excitability in a single ventricular fiber ARP and TRP represent the end of the absolute and total refractory periods.

The relative refractory period in turn, extends from this time until shortly after the transmembrane potential attains the normal resting value Furthermore, when the response of the fiber is recorded by means of an intracellular electrode the magnitude and shape of the action potential elicited by stimulation during the relative refractory period is seen to vary in accordance with the level of the transmembrane potential. The earliest

Weidmann (1955a) has employed the voltage clamp technique (Hodgkin and Huxley, 1952b) discussed in Chapter II to study the effect of transmembrane potential on the ability of Purkinje fibers to undergo an increase in sodium permeability In this work he employed the maximum rate of rise of the action potential as an indicator of the inward sodium current The results obtained demonstrate that there is an s shaped relationship between a steady level of membrane potential and the maximum rate of rise of the action potential resulting from stimulation (Fig 27 B) Thus, while at resting potentials greater than 90 mv the rate of rise is maximal, at a membrane potential of 70 mv it has fallen to one half and at a potential of approximately 50 mv it is less than 10 per cent of maximal These changes in rate of rise follow changes in the membrane potential with a time constant of less than 20 msec

This relationship is seemingly responsible for the inability of the fiber to respond to stimulation during the absolute refractory period, since if there is no inward sodium current, there can be no action potential Furthermore, the same property of the membrane can explain in part the elevated thresholds observed during the relative refractory period During repolarization, when the transmembrane potential is low (60 70 mv), a stimulus of normal threshold intensity results in a small depolarization, this depolarization, however, causes only a negligible change in sodium current and an action potential fails to appear Stimuli much stronger than this, on the other hand produce far greater depolarization of the membrane, this marked lowering of the membrane potential ensures that the maximum sodium current of which the fiber is capable under the existing conditions will occur When, due to the level of membrane potential, this inward sodium current is adequate, a propagated action potential is formed As repolarization proceeds towards completion, progressively smaller depolarizations by the stimulus will cause an adequate sodium current and thus a propagated action potential It is also possible that there is an augmented outward potassium current during repolarization as has been demonstrated in certain nerve fibers (Hodgkin and Keynes, 1954) If this is the case, then part of the requirement for increased stimulus intensity during the relative refractory period is due to this factor, since the repolarizing effect of the outward K^+ current opposes the depolarizing action of the stimulus and of any resulting inward sodium current

The preceding discussion can be summarized in rather general terms

in Fig 27 D where it can be seen that the time-course of repolarization and subsequent slow diastolic depolarization gives rise to the following changes in current strength required to stimulate Towards the end of repolarization, when the transmembrane potential is only slightly greater than the threshold potential, the stimulus intensity is minimal. Subsequently as the membrane potential attains higher values the current strength required to stimulate increases Finally, when the fiber begins to depolarize once more, the stimulus requirement is again diminished In terms of the stimulus intensity required throughout diastole the initial low value can be referred to as supernormality A consideration of the relationship between resting membrane potential and threshold discussed above provides an adequate explanation for these observations.

DIPS AND REPOLARIZATION OF SINGLE FIBERS

The presence of irregularities or dips in the course of the recovery of excitability of the heart has been described in Chapter IV and the association between these dips and both an enhanced vulnerability to fibrillation and also an increased effectiveness of anodal stimulation has been noted (Orias et al. 1950) No irregularity is recorded in the recovery limb (repolarization) of the single fiber action potential at a comparable interval in time (Fig 24, 25) Furthermore in the papillary muscle under normal conditions there is no clearly defined interval during repolarization when test stimuli will produce repetitive firing However when the dog's papillary muscle has been treated with veratrine (Matsuda *et al* 1953) or when acetylcholine has been added to preparations of auricular muscle (Hoffman and Suckling 1953-a) it is possible to elicit multiple *extrasystoles* and runs of rapid, spontaneous activity by means of suprathreshold stimuli applied at one interval during the repolarization limb of the recorded action potential. This occurs despite the absence of any detactable irregularity or sign of such a period in the recorded transmembrane action potential. Under these conditions moreover even stronger stimuli applied at other intervals result in only single extrasystoles Thus a period characterized by a peculiar susceptibility to the production of multiple firing by a single stimulus pulse can be demonstrated even in isolated preparations of heart muscle at a critical instant during recovery

It is possible that the dips and associated vulnerability (see Chapter VI) result from some process occurring in each fiber or from certain

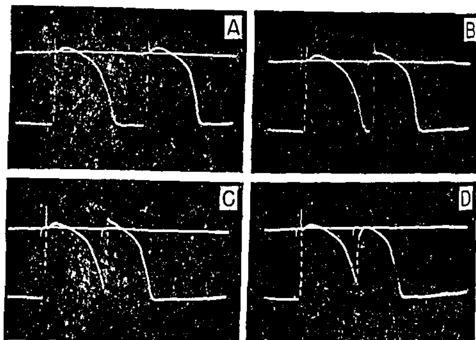


FIGURE 30 Change in shape and magnitude of propagated ventricular transmembrane action potentials at various times during and after repolarization Time of application of stimuli indicated by artefacts on baseline Stimulation during late diastole (A) late relative refractory phase (B) early relative refractory phase (C) and at the border of the absolute refractory period (D) Compare with figure 27C (Retouched to show action potential upstrokes by dotted lines)

effective stimuli produce an action potential which not only rises slowly but also is decreased in both duration and magnitude (Fig 27 C, 30 A, D) Action potentials elicited progressively later during the recovery process are of increased voltage and duration until, when the transmembrane potential is fully restored, the action potential is of normal magnitude Even at this time, however, the duration is less than would be expected, this accelerated repolarization of premature action potentials is discussed in Chapter VIII

SUPERNORMALITY In the preceding chapter a brief period of supernormality (i e , excitability somewhat greater than the resting level) was reported to occur in the auricle and ventricle of some hearts A similar period has not been found in studies of isolated papillary muscle However, in single fibers of the Purkinje system Weidmann (1955a) has demonstrated a short interval of supernormal excitability during the terminal phases of the repolarization process His results are reproduced

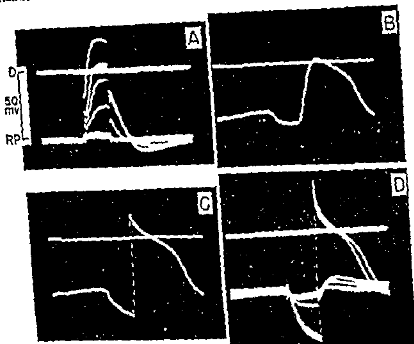


FIGURE 31 A—Shows ineffectiveness of all intensities of cathodal stimuli of long duration in the partially depolarized ventricular cell.

B, C, D—show repolarization during long anodal stimuli with origin of a response on the break of the anodal current. Note that the magnitude of the response is proportional to the degree of hyperpolarization induced by the test pulse. (Retouched to show action potential upstrokes by dotted lines.)

effect of anodal current on a single fiber of the dog's Purkinje system and the initiation of break excitation

On the basis of these findings it can be postulated that the late or major dip in the strength interval curve of the intact heart occurs in the following manner During diastole excitation takes place under the cathode because it is normally the effective timulus and because although anodal break excitation can occur in diastole much higher current trengths would be required As the test stimulus is advanced progressively earlier into the relative refractory period stronger cathodal currents are required because of the changes in sodium current and threshold potential discussed above. At this time, when the membrane is partly depolarized the current flow under the anode will cause a local repolarization and thus

particular interrelationships between several or many fibers Any attempted explanation of the nature of the vulnerable period and of the major dip in the excitability curve of the intact heart must include a consideration of the following phenomena that are intimately related to this phase of the recovery process 1) the temporary lowering of thresholds during the dips which represents an actual momentary increase in excitability to test stimuli, 2) the origin of propagated excitation from the immediate vicinity of the anode during this interval 3) the demonstrated increase in susceptibility to anodal stimulation during a part of the repolarization process, and 4) the observation that vulnerability to multiple firing and fibrillation resides in this interval of the recovery process These several phenomena may or may not be interrelated, it is most likely, however, that all have their origin in a common aspect of the recovery process

LOW THRESHOLD DIP Records obtained from single fibers by means of intracellular microelectrodes have provided some evidence that can be brought to bear on this problem, and a possible explanation of the temporary *lowering of thresholds* during the major, or low threshold dip can be attempted This explanation depends on the known effects of anodal current on the cell membrane

It has been demonstrated in numerous experiments that anodal break excitation can occur (see Chapter II) However, it does not often occur under normal resting conditions and always requires a greater current flow than does the corresponding cathodal stimulus Furthermore, numerous experiments on single fibers of cardiac muscle have shown that anodal current repolarizes the membrane under a wide variety of conditions (Weidmann, 1951, Coraboeuf, et al, 1954, Hoffman and Suckling, 1955) In addition Weidmann has shown quite clearly (1951) that anodal polarization of the membrane, applied even during the upstroke of the action potential, can result in either of two phenomena depending on the *current intensity employed Weak currents increase* the transmembrane potential during the current flow and elicit graded spikes of depolarization on the break Stronger currents in excess of a certain definite value, produce a complete repolarization that persists even after the current *flow ceases and is propagated along the membrane* at a finite velocity Earlier workers have similarly demonstrated propagated repolarization resulting from strong anodal current in the hearts of frogs and turtles (Schiff, 1850, Biedermann, 1895) Figure 31 A, D shows the repolarizing

progressively earlier in the relative refractory period, little change in latency of response is revealed (Fig 27 C, D) Identification of a propagated action potential by means of a single electrode, however, is not always reliable. It has been found by Grundfest et al. (1954) that when a giant squid axon is stimulated during periods of refractoriness a response showing an actual overshoot but which is not propagated will occur All-or nothing propagation is not necessarily indicated by occurrence of a spike like response near the stimulating electrode Nevertheless, this observation that in individual heart cells latency of response at various intervals of the refractory period remains about the same unless strength and duration of stimuli are changed, suggests that the increase in latency noted in studies of the intact heart is due primarily to a slowing of conducting when the action potential is initiated in partially recovered tissue. This certainly is the case if consideration is limited to stimuli of a reasonable range of intensities On the other hand, as mentioned previously very strong test pulses may create a local tissue polarization which persists for some time and then stimulates after the recovery of excitability has been completed. In such cases the very long latency noted is merely a measure of the time required for recovery of excitability to reach resting levels

The observation that suprathreshold pulses whether applied during diastole or late in the relative refractory period, cause a decrease in latency is also explained by the nature of the local response and the action potential. A stimulus of just threshold intensity produces a partial depolarization of the fiber membrane This depolarization causes an increase in sodium permeability and a further depolarization, and this so-called regenerative reaction proceeds with an increasing velocity until the rapid upstroke of the action potential is formed If, on the other hand a suprathreshold stimulus is employed the transmembrane potential is lowered almost instantaneously to a very low value, maximum sodium permeability results almost immediately and the latency between application of the test shock and appearance of the action potential is thereby decreased

The decreased latency associated with the action potentials originating in the anodal surround when test pulses are applied during certain parts of the relative refractory period probably results from the fact that the local repolarization induced by the anodal current increases excitability and also from the fact that this increased excitability increases the conduction velocity to normal values.

a restoration of excitability If cathodal current is not able to stimulate readily this repolarization effect is able to occur Subsequently, on the break of current flow excitation may occur in the anodal surround.Several findings are at least compatible with this hypothesis, these are 1) the apparent onset of activity close to the anode during the major dip, 2) the change in latency usually associated with test shocks applied at this interval of the cycle, and 3) the observation that very short pulses fail to stimulate during the interval when the major dip is found In addition, the association between the dip and vulnerability to fibrillation might well result from the local inhomogeneity of the myocardium, with respect to both conduction velocity and level of excitability, that results from the repolarizing effect of anodal current flow In regard to this, it has been shown that anodal current is more effective than cathodal in producing fibrillation (Harris and Moe, 1942)

The shape of the typical strength interval curve suggests that perhaps two different modes of initiation of activity are operative during the recovery process Early during the relative refractory period the current strengths required to stimulate are often one hundred or more times greater than the resting or diastolic threshold Furthermore, the transition from these extremely high thresholds to the low intensities needed during the major dip is quite abrupt It is thus possible that activity in response to early, very strong stimuli occurs because these pulses create a local polarization of the tissue which persists until recovery has been almost completed (Harris and Moe, 1942) The apparent inability of the anode to cause repolarization and break excitation at this time might well result from the production, at these high current strengths, of propagated repolarization originating in the anodal surround A similar explanation may cause the "nothing" phenomenon that has been discussed in Chapters IV and VI However, the experimental evidence presently available is not adequate to test either of the above possibilities

LATENCY AND THE LOCAL RESPONSE The statement has been made in the preceding chapter that the most adequate method of measuring true latency is to record from the same area of membrane through which the stimulus current is passed as well as from more distant leads *This method of recording near the stimulating electrode* has beeen employed in studies of the single fiber activity in the Purkinje system (Weidmann, 1955 a, b) When an intracellular microelectrode is used to record the response of the membrane to stimuli applied during *diastole and*

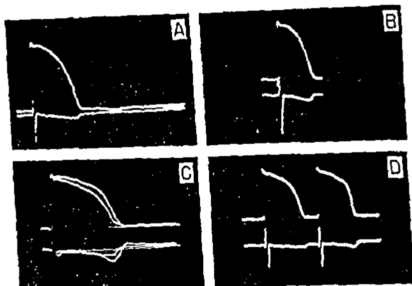


FIGURE 32. Relationship between the transmembrane action potential and the unipolar electrogram. A and B show the effect of heart rate C and D show the effect of extrasystoles. See text for discussion.

is associated with an increase and slow repolarization with a decrease in the voltage of the T These two types of change in the repolarization process—early or late initiation and slow or rapid time course—may vary in the same or opposite direction In either case the appropriate T wave change is recorded This is clearly shown in Figure 32 C which portrays the first two action potentials recorded on initiation of activity from a single fiber of a previously *quiescent* papillary muscle The first action potential reveals a long plateau and rapid repolarization and the simultaneous electrogram T wave is late and large. The plateau of the next action potential is shorter and repolarization more gradual the simultaneous T deflection is early and shallow A similar relationship between the timing and magnitude of the *auricular* T wave and the transmembrane potentials of the auricle is seen in Figure 25

These records demonstrate *that* the position and magnitude of the T deflection of the unipolar electrogram are directly influenced by the course of membrane repolarization. These simple relationships do not exclude the effect of other factors such as the temporal dispersal of activity in the

RELATIONSHIPS BETWEEN CARDIAC MEMBRANE POTENTIALS AND THE UNIPOLAR ELECTROGRAM

It is not within the scope of this work to discuss in any detail the various theories which attempt to explain the genesis of either the cardiac electrogram or electrocardiogram However, since these records are most frequently employed to study the propagated responses of heart muscle, it is pertinent to comment upon certain relationships between cardiac membrane potentials and the local unipolar electrogram which have been demonstrated by recording the electrical activity of single fibers (Hoffman and Suckling, 1953a, 1954)

The temporal relationship between the R wave of the unipolar electrogram and depolarization of the muscle membrane and between the T deflection and repolarization has been mentioned in previous sections (see Fig 24) and applies equally well in the case of both auricular and ventricular muscle As shown in Figure 32 A when the local unipolar electrogram is recorded from the surface of the muscle immediately adjacent *to the site of the intracellular microelectrode* the upstroke of the transmembrane potential record and the rapid positive negative intrinsic deflection of the electrogram R wave are inscribed simultaneously When, on the other hand, these two electrodes are more widely separated, the *intrinsic deflection either precedes or follows the evidence of depolarization recorded by the intracellular electrode* These records thus offer conclusive evidence in support of the concept (Lewis, 1925, Wilson et al, 1933, MacLeod, 1938) that the intrinsic deflection of the semidirect unipolar electrogram signals the occurrence of depolarization in the muscle directly subjacent to the stigmatic electrode

It has been possible to further evaluate the causal relationship between depolarization and repolarization of the excitable membrane and the electrogram deflections by recording changes produced in the latter record when the time course of membrane activity is varied

When only the duration of the ventricular action potential is altered (as by changes in heart rate) and the time course of depolarization and repolarization remains the same, the only change produced in the simultaneous local unipolar electrogram is in the duration of the R T interval *The earlier recovery of membrane polarity seen at fast rates is associated* with an earlier, simultaneous T deflection (Fig 32 A, B) When, however, the rate of repolarization of the cell membrane changes, the *amplitude of the T wave is altered* As seen in Figure 32 C, *rapid repolarization*

polarization and the height of the threshold potential are among the factors involved.

The relationship between excitability and the transmembrane action potential has been determined. During the refractory period much stronger currents are needed to induce an inward sodium current adequate to excite the cell by reversing the polarizing processes underway Absolute refractoriness persists following activity until repolarization is approximately half completed

A period of supernormality occurs during the terminal phase of the transmembrane action potential. This is clearly identified by transmembrane recording

Studies of the effects of applied anodal and cathodal current on transmembrane potential have shown that anodal current aids in repolarization of the membrane and may shorten the period of relative refractoriness Cathodal current has only a depolarizing effect.

The relationship of cardiac membrane potentials to the unipolar electrogram is described and information derived from studies of the transmembrane action potential concerning the dip phenomenon, vulnerability to fibrillation and latency of response is discussed

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muscle, which also influence the form of the T deflection They do, however, indicate the degree to which the unipolar electrogram reveals the time course of depolarization and repolarization in cardiac muscle

SUMMARY

The superiority of the direct micropuncture technique to the indirect or surface recording methods for measuring transmembrane potentials becomes obvious when the two techniques are compared The action potentials recorded by means of intracellular electrodes are somewhat different in ventricular and auricular fibers of the dog heart The ventricular cell potential shows a long lasting plateau phase which is responsible for the slower rate of repolarization Simultaneous recordings of transmembrane action potentials and the cardiac electrogram show that the rising phase and overshoot of the cellular potential corresponds to the R wave while the fast terminal phase of membrane repolarization coincides with the T wave of the electrogram

Recording of transmembrane potentials from specialized tissues such as the Purkinje fibers gives information concerning pacemaker activity The microelectrodes record the spontaneous depolarization which begins as soon as repolarization is attained following activity A propagated action potential is initiated when this local depolarization reaches a critical level This potential of instability is referred to as the threshold potential because when this degree of depolarization is attained a regenerative process is touched off which brings about further depolarization and a reversal of potential

Theories advanced to explain the resting and action potentials and membrane repolarization on the basis of ion flux provide an adequate explanation of most phenomena observed in the heart cell The magnitude of the reversal and the rate of rise of the action potential vary as predicted when extracellular sodium concentration is changed Although repolarization probably involves an outward flux of potassium the unique time course of recovery in cardiac muscle suggests that additional, if not completely different mechanisms must be operating than those thought to bring about repolarization and restore a normal resting potential in nerve

Spontaneous rhythmicity appears to originate in the instability of the membrane of pacemaker tissue Various influences are found to affect the rate at which a pacemaker fires Changes in rate of spontaneous de-

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VI The Production and Nature of Fibrillation

Current theories of fibrillation and the circumstances favoring and producing this type of arrhythmia are discussed A new concept of causative factors is considered Vulnerability to fibrillation and the location of the vulnerable period in the cycle fibrillation thresholds defibrillation the "nothing-phenomena" and other matters pertaining to abnormal responses of the heart are described

NORMAL FUNCTION OF THE HEART depends upon coordinated rhythmic action of all its parts Efficient integration of the contraction of heart muscle elements is necessary to develop the required tensions and to maintain a sequence of events which will enable the heart to operate as a pump The energy for the maintenance of arterial blood pressure and flow comes directly from this organ The ejection force establishes the required pressure gradient and the concomitant cardiac output supplies the tissues with needed materials Cessation of effective heart function may result from anatomical defects, failure of venous return of blood, failure of rhythmic excitation loss of contractility or breakdown of the integrating factors maintaining cooperative activity of heart elements Abnormalities of excitability, of conduction and of the intrinsic excitatory processes of heart cells can give origin to the latter types of functional impairment. A consideration of cardiac arrhythmias and responses to stimulator influences is therefore pertinent to the theme of this monograph

MAINTENANCE OF NORMAL CARDIAC RHYTHMS

THE ROLE OF THE PACEMAKER The heart is actually comprised of many potentially autonomous units Not only can its component chambers beat independently but also all cardiac cells possess an ability to contract rhythmically Any portion of the heart can be excited intrinsically or extrinsically by applied stimuli and an impulse thus initiated can travel in any direction since cardiac cells are interconnected by protoplasmic bridges Normal coordinated activity is initiated by pacemakers so located that non specialized conduction pathways connected therewith bring

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that the site of initial negativity moved about within the sinoauricular node indicating some lack of absolute dominance there but for the most part the beat originates in the mid portion of this structure (Prinzmetal et al. 1952) Variations in rhythm of beat origin are sometimes so gross as to be apparent to the casual observer sinus arrhythmia is a well known phenomenon (Anrep et al 1936 Lepeschkin 1951) Even in the most regularly beating hearts there are fluctuations of a few milli-seconds in cycle length detectable by exact measurement and the regularity of the rhythmic activity of pacemakers is subject to modification by neural, chemical and physical influences (Chapters VII VIII X) Substantial variations in sinus rhythm are possible without escape of other pacemakers

THE ORIGIN OF ARRHYTHMIAS The term arrhythmia is applied to a considerable number of abnormal occurrences The well known facts can be stated briefly as follows. Permanent or long lasting dominance of the heart by other than the normal sinoauricular pacemaker produces an abnormal sequence of electrical and mechanical events This may be due either to a decreased pacemaker rate to suppression of impulse generation by the normal pacemaker or to enhanced frequency of impulse formation in an ectopic focus In the former case the heart rate will be slower and in the latter faster than normal. The atypical rhythm established may be quite regular Theoretically beats can originate in any part of the auricle or ventricle but there is a hierarchy of potential pacemakers in the heart and it can be predicted that if the S A node is destroyed the A V node will assume the pacemaker role The A V bundle serves as a conduction pathway between auricle and ventricle and when it is severed these two chambers beat independently The tissues which constitute the special conducting system of the heart have a greater intrinsic rhythm than the primarily contractile tissue and when the sinoauricular node and the A V node are inactivated the ventricular beat tends to originate in the A V bundle or in some lower segment of this specialized conducting system.

There are exceptions to this general rule and the normal rhythm of the heart can be interrupted by extrasystoles which may originate in practically any portion of either the auricle or ventricle. If the extrasystole occurs early in the cycle, especially in a slowly beating heart, an interpolated beat results because the myocardium recovers normal excitability again before the next systole is due Such interpolated beats cause no readily perceptible interference with the heart's mechanical functions If

the various components of the organ into action in an appropriate sequence

There can be no doubt that the beat of the heart in vertebrates is of myogenic origin (Lovatt Evans p 549, 1952) After each beat the heart passes through a regular series of recovery phases attaining normal excitability Each new cycle of electrical and mechanical events results from a wave of excitation which sweeps over the heart from its site of origin in the pacemaker stimulating all cells before intrinsic firing occurs

Intracellular recording by means of microelectrodes has shown (Draper and Weidmann, 1951, Brady and Hecht, 1954, Hutter and Trautwein 1955) that in cells serving a pacemaker function, depolarization does begin as soon as repolarization is completed When this local excitatory process (slow spontaneous diastolic depolarization) has resulted in a critical level, a propagated impulse is initiated which gives rise to the next heart beat It is not known whether the excitatory process is merely a gradually developing instability of the polarized state of the membrane brought about by the decay of polarizing forces, or whether it is a new set of metabolic phenomena which stand in opposition to the processes working toward the production and maintenance of membrane polarization (Chapter II and V) It is known, however, that when a heart cell is depolarized before its intrinsic excitatory process has attained an effective intensity, the build up of this process must start again from the initial level Heart cells are thus dominated and driven by pacemakers possessing a higher intrinsic frequency

The rhythm of events in the mammalian heart is normally established by a pacemaker located within the sinoauricular node (Eyster and Meek, 1921) Rijlant (1928) and others (McWilliam 1888 a, Erlanger, 1913 Geraudel, 1935) have described presinus sites of beat origin but it has *been demonstrated beyond a doubt that the excitatory process* occurs in or near this specialized structure even when it is transplanted to a different site in the auricle (Rijlant 1927) This pacemaker is the cardiac tissue which normally possesses the highest rhythmicity it originates waves of excitation which pass throughout the heart initiating activity of all other heart cells before their intrinsic processes would normally have caused them to contract

The heart beats with a regularity and at a rhythm determined by processes within its pacemaker *The regularity of the rhythm of pacemaker tissue* varies somewhat. Eccles and Hoff (1934 a and b) observed

A DESCRIPTION OF FIBRILLATION AND ITS RELATION TO OTHER ARRHYTHMIAS

Fibrillation is a state of rapid and disorganized activity of the elements comprising the myocardium It is an arrhythmia which demonstrates the ultimate disorganization attainable

AURICULAR FIBRILLATION AND FLUTTER Very fast regular atrial rhythms of 350 to over 500 beats/min can be sustained for long periods of time. Under these conditions because of the limited possibilities for conduction in the A V bundle not all of the auricular beats are followed by ventricular responses The very rapid action imparted to the auricles at such rates was called atrial or auricular flutter by McWilliam (1888-b) Ritchie in 1905 using venous pulse tracings showed that an atrial flutter similar to that produced *experimentally in dogs* occurs clinically When these rapid auricular rhythms become somewhat irregular the descriptive term applied may be either "impure" or "irregular flutter" or even "coarse fibrillation" depending *upon the* extent of irregularity of the electrical events recorded in the electrocardiogram

Auricular fibrillation is a state in which disorganization of *activity is* so great that the auricles lose their ability to forcibly eject blood into the ventricles They become distended not from loss of activity of the muscular elements in their walls but because the muscular elements are not acting in unison The auricular fibers individually considered, display a very fast regular or irregular *rhythm* of contraction unrelated to that of any other fibers Occasionally a sufficient number of these independently acting elements beat in phase to give electrical and mechanical waves which travel for short distances over the atrial *surface* but these are never effective enough to produce an *ejection* of blood or a relief of the venous congestion In auricular fibrillation as in auricular flutter the ventricle cannot follow the very fast bombardment of impulses coming from the auricles Because of combined effects of A V bundle and ventricular refractoriness the ventricle s action becomes grossly irregular

The identity of auricular fibrillation first produced experimentally by Vulpian in 1874 with the clinical condition termed *delirium cordis* was demonstrated by Rothberger and Winterberg (1914-16) and by Lewis (1918) Protection of the ventricle from this bombardment of impulses from the fibrillating auricle by increasing the degree of A V block is desirable and is a logical aim of therapeutic measures (Salter 1952), provided the auricular fibrillation cannot be terminated.

an extra beat occurs late in a cycle, however, the refractoriness induced thereby does interfere with normal beat origin (auricular extrasystole) or conduction (ventricular extrasystole) and there is a "compensatory pause" until another beat can originate in the pacemaker This latter occurrence does impair the regularity of the heart's pumping action Extra systoles can be thought of as originating from competitive pacemakers and if this competition persists, multiple extra impulses are created Sustained action of the ectopic pacemaker can cause a very rapid heart rate as occurs in paroxysmal tachycardia and probably also in auricular flutter (Wiggers, 1949, Prinzmetal et al, 1952, Hecht et al, 1953) Multiple extrasystoles originating either from a single focus or several foci may so interfere with normal pacemaker dominance that serious disorganization of heart action results

For purposes of discussion a convenient gradation of abnormalities can be made starting with sinus tachycardia, through paroxysmal tachycardia, auricular flutter, impure or irregular flutter to auricular fibrillation Sinus tachycardia follows release of the S A node from vagal inhibition or may be induced by acceleratory nerve stimulation or the direct action of drugs on this pacemaker tissue (Wiggers, 1949) Paroxysmal tachycardia of atrial origin is differentiated from sinus tachycardia by its more rapid onset and cessation and greater regularity The rates attained are higher than the S A nodal rhythms as though an irritative process acting elsewhere than in the sinus induces such a rapid origin of beat that this region suddenly takes over the pacemaker function from the more slowly acting S A node It has also been suggested that competing distinct pacemakers might, between them, double the rate of heart beat. Para arrhythmias do occur in the heart (Kaufmann and Rothberger, 1920) but the coupling of beats to produce tachycardia can also be explained on the basis of reentry Very rapid multiple firing can originate from either a persisting sink or local excitatory processes of various types (Chapter II), and one need not evoke either multiple foci or circus movement hypotheses to explain paroxysms of rapid beat origin unless evidence of such occurrence is found (Hecht et al, 1953) It can be said, however, that these arrhythmias which vary from simple interruptions of normal rhythm by occasional extra beats to complete disorganization of the myocardial activity, are due either to intrinsic or extrinsic abnormalities which interfere with the normal conduction of impulses or create ectopic foci of excitation

this particular state of activity in the auricle Fibrillation in the ventricle as in the auricle is an incoordinated type of contraction producing no useful beats The ventricles dilate and groups of muscle fibers appear to contract independently of adjacent segments of the myocardium imparting a vermicular movement to the chamber walls (Wiggers and Wegria 1940) This arrhythmia at its inception is not an all or none state The incoordination may first involve comparatively large sections of the myocardium and then progress by a fractionation of activity into smaller and smaller independently acting areas. Fibrillation may thus develop out of a series of multiple extrasystoles and a temporary state of flutter like activity

In attaining the true fibrillatory state there is a progressive multiplication of the fragmentation and the elements beating in unison become fewer and fewer but even in the ultimate stages of fibrillation it is doubtful that all fibers are beating independently small fiber groups are contracting out of phase with other groups and there is often a wave like motion imparted to the surface of the ventricle (Wiggers 1940) Recording of the activity of single elements in the myocardium of fibrillating hearts by intracellular electrode leads shows that these elements may either be contracting at very fast regular rates as indicated by action potentials of a uniform amplitude and spacing or their activity may be varied in that action potentials are not regularly spaced nor of uniform size and duration (Hoffman and Suckling 1955) (Figure 33)

A great deal has been written concerning the etiology and the nature of flutter and fibrillation and the numerous theories held have often been discussed and reviewed (Lewis 1925 Wiggers 1940 Scherf et al 1953 Hecht et al. 1953) One certainty is that in these conditions no single pacemaker dominates the heart at all times by initiating a rhythm of activity which all other elements can and do follow Further discussion of the cause and nature of fibrillation and allied arrhythmias will be delayed until the results of various new experimental studies have been presented.

VULNERABILITY OF THE HEART TO FIBRILLATION

The existence of a vulnerable period during which applied stimuli are likely to produce fibrillation of the heart has been recognized for a number of years DeBoer (1920-21) showed that a process similar to fibrillation in mammalian hearts could be induced in the frog s ventricle

VENTRICULAR FIBRILLATION Ventricular fibrillation was first described by Erichsen in 1842 and Hoffa and Ludwig in 1850 but Vulpian in 1874 first used the name fibrillation (mouvement fibrillaire) to describe

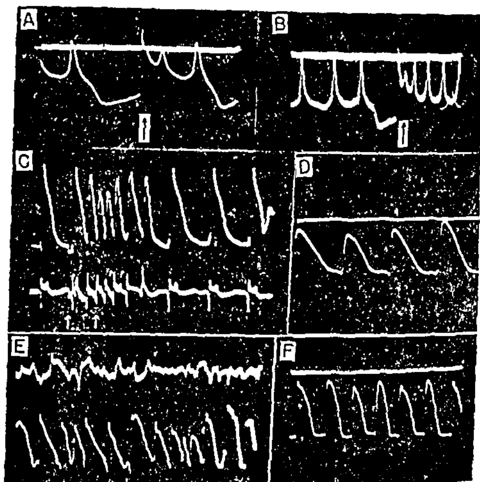


FIGURE 33 Single fiber activity during fibrillation

A and B Spontaneous repetitive activity in a Purkinje fiber Arrow indicates origin of action potential Note repetitive incomplete depolarizations during recovery

C Auricular tissue showing normal action potentials and irregular activity during fibrillation induced by stimulation (arrows) Lower tracing is the electrogram.

D Activity of single ventricular fibers during fibrillation induced by anoxia.

E Single ventricular fiber activity during fibrillation produced by stimulation of ventricular myocardium Electrogram shown in upper tracing

F Cellular action potentials during fibrillation produced by KCL.

Records A, B from isolated tissue C D E, F obtained from intact hearts in situ. Time marks at 50 msec in A and F

Hoffman et al, 1951 1955) There appears to be no question that vulnerability is associated with the recovery of excitability and the repolarization of heart cells following a propagated beat. The question remaining is, during what interval or intervals of this recovery period is the heart vulnerable to fibrillation

Techniques employed to study the state of excitability throughout the cycle are applicable to the localization of phases of the cycle during which the heart might be vulnerable to the production of fibrillation by electrical stimuli Stimuli of varying suprathreshold intensity and different durations can be applied at all intervals of the cycle to determine the state of the heart s vulnerability (Orias et al. 1950-a, Brooks et al 1951) If at any period fibrillation results the heart can be defibrillated by countershock and the testing continued Such studies have been conducted and the results are as follows

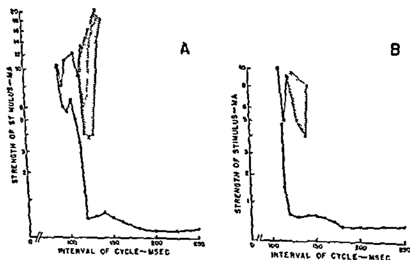


FIGURE 34. Auricular strength interval curves (•—•) of dog (A) and cat (B) showing thresholds for multiple extrasystoles (x——x) fibrillation (x x) and no response (o——o) The cross hatched area is the vulnerable period

VULNERABILITY OF THE AURICLES TO FIBRILLATION Results obtained in a study of the dog auricle are shown in Figure 34-A At no period in the cycle do stimuli of *threshold strength* produce either multiple extrasystoles or fibrillation Furthermore at no time during the super normal phase or other periods of diastole is it possible to produce fibrill

by single induction shocks applied near the end of mechanical systole He thought that this response was peculiar to the hypodynamic state of the heart at that period Andrus, Carter and Wheeler (1930) found also that a single induction shock could cause fibrillation of normal auricles of dogs More definite statements concerning the possibility of producing fibrillation by single shocks of short duration were made by King (1934) and Ferris et al (1936), who reported that shocks of 0 03 second duration were effective in fibrillating the ventricle They also pointed out that to accomplish this the shock had to be applied during the occurrence of the T wave of the electrocardiogram, an event which they associated with the relative refractory period Wiggers and Wegria *(1940) greatly expanded this observation and demonstrated 1)* that a considerable portion of late systole constitutes a *vulnerable period* during which stimuli (single induction shocks or condenser discharges) are effective in inducing ventricular fibrillation, 2) that vulnerability is inherent in normal hearts and 3) that the elicitation of fibrillation during this period does not require the passage of current through *all portions* of the myocardium Later they found (Wegria and Wiggers, 1940) that weak induction shocks applied during the vulnerable period elicited only early premature contraction but if shocks were increased in strength, fibrillation resulted Such shocks applied during diastole never produced fibrillation Subsequent work by Wigger s group (Wegria, Moe and Wiggers, 1941) gave additional support to the concept of the existence of this *vulnerable period* and also located it in the latter part of systole, a time during which some fibers are in and others *have passed out* of a refractory state (Wiggers, 1949, text p 573)

Despite this evidence that the vulnerable period is a phenomenon of late systole and the terminal phases of the refractory period, there still remain in current textbooks statements to the effect that when a shock falls just outside the absolute refractory period of the auricle or ventricle these tissues are likely to fibrillate (Lovatt Evans 1952) This seeming contradiction between localization of the vulnerable period early or late *in the relative refractory period* can be resolved but statements to the effect that fibrillation may be initiated most readily by weak electrical stimulation at the point in the cycle when the heart tissue is least refractory (Soderman, 1950 p 83), *as though the period of vulnerability coincides* with the phase of supernormal excitability, are not supported by recent evidence (Orias et al, 1949, 1950 a and b, Brooks et al, 1951,

is the expected response (Hoffman et al., 1951). Figure 34-B shows a correlation between the dip area of the small mammalian auricle and the period during which multiple auricular extrasystoles can be elicited. An explanation of the fact that during the vulnerable period a stimulus as its strength increases can produce various effects, namely a single extrasystole, multiple extrasystoles, fibrillation or at very high intensity no response at all, will be offered later.

VENTRICULAR VULNERABILITY. The existence of a period of vulnerability to fibrillation was discovered first in studies of the ventricle. Inasmuch as the recovery process lasts longer in the ventricle than in the auricle, often showing two well defined dips, this provides opportunity to study in some detail the relationships between these irregularities in the recovery curve and vulnerability to fibrillation. This will be done in the following paragraphs on the basis of the work of Hoffman et al. (1951, 1955).

1. *Dog Heart.* The dog's ventricle is readily fibrillated by the application of a single test shock when this falls within the *major dip area* of the recovery curve (Figure 35 A through C; see also Table 4). Prior to *and following* the dip areas, even shocks of maximal duration (15 msec.) and high intensity (20-30 ma.) can be applied with impunity. Spontaneous

TABLE 4.—*Relationship between Vulnerability and the Major Dip in the Dog Ventricle*

Exp	Cycle Length, msec.	Interval of Cycle		Position in Cycle of lowest threshold		Total Refractory Period Position in Cycle
		Dip	Vulnerability*	Dip	Fibrillation	
6/24/53	250	115-140	115-125	125	120	150
12/22/53	250	115-130	120-125	125	120	145
7/8/53	300	100-115	110-115	105-110	115	120
7/8/52	250	90-105	85-95	100	90	120
7/16/53	250	100-115	100-1[illegible]0	105	110	130
6/26/53	250	110-140	115-130	125	125	160
4/21/53	300	120-160	125-150	150	150	180
7/10/53	300	140-150	135-150	145	145	170
5/15/53	250	1[illegible]0-140	105-120	130	115	150
10/13/53	250	125-140	125-130	130	130	150
5/8/53	300	140-160	125-1[illegible]5	150	130	160
2/2/54	300	110-130	95-115	120	110-115	140

*In all cases the range of vulnerability is that determined with a short-duration stimulus (1-3 msec.).

ation by stimuli varying in duration between 0 1 to 15 0 *msec and from* 0 1 to 35 0 ma in intensity It can be shown, however, that the auricle is vulnerable to fibrillation only during a certain phase of the relative refractory period (Orias et al, 1950, Brooks et al, 1951) If the strength of the stimulus acting at these particular intervals of the cycle is gradually increased in intensity, single extrasystoles, multiple responses and brief periods of flutter or fibrillation occur The duration of the runs of extrasystoles vary somewhat with the duration and strength of the testing shock but once initiated fibrillation lasts at least several seconds regardless of stimulus strength and frequently persists until terminated by massive stimulation (countershock) or some other procedure On the other hand, very strong shocks may produce no response at all when applied during the vulnerable period but this phenomenon will be discussed later

As shown in Figure 34-A, the vulnerable period coincides with the major dip of the strength interval curve of the dog auricle (Brooks et al, 1951) Long duration test shocks (13 15 msec) give a less precise delimitation of the vulnerable period than do stimuli of 1 3 msec in duration, nevertheless all stimuli show vulnerability to exist during this same period of the cycle Pulses of very short duration do not stimulate the heart early enough in the cycle to reveal the dips (the vulnerable period) and the briefest stimuli which do show the presence of dips are not effective enough in some instances to provoke fibrillation *The thresholds for* fibrillation and the production of multiple extrasystoles are never as *constant as are those for single extrasystoles* Repeated stimulation at the threshold strength for fibrillation may at times give only multiple extrasystoles The fact that both types of response can be evoked from the same period of the cycle suggests that the production of repetitive firing and fibrillation originate in the same basic processes (Harris and *Moe, 1942)*

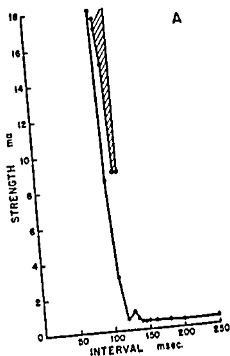
It may be added here that it is difficult to produce fibrillation of long duration in the small dog auricle and almost impossible to produce it in the even smaller cat auricle by *means of single shocks of* 0 1 to 13 0 msec duration and of 0 25 ma in intensity Both the cat and dog auricle show dips in the curve depicting the recovery of excitability however, and can be fibrillated by tetanizing currents of low intensity or by single shocks when the tissue is cooled Single shocks of high intensity produce in the cat auricle only multiple extrasystoles at a time when vulnerability

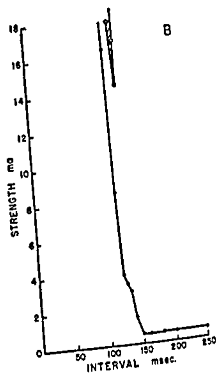
defibrillation rarely occurs in the dog's ventricle however, and defibrillation by means of a countershock is thus necessary if the study is to continue (see Chapter IX)

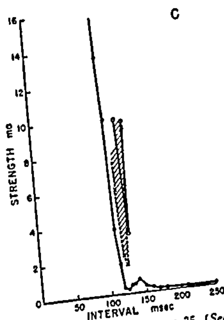
Test shocks of long duration frequently show an early and a late dip during the relative refractory period as well as a long lasting supernormality after recovery from refractoriness In such cases it is sometimes possible to demonstrate two periods of vulnerability (Hoffman et al. 1955) one during the late or major dip and another characterized by a considerably higher threshold at the earlier interval of the recovery process where the first dip occurs Vulnerability is normally greatest during the late or major dip under conditions maintaining in these experiments However it has recently been reported that in the cooled heart vulnerability to fibrillation is greatest during the phase of the cycle showing the first or early dip (Hegnauer and Covino 1955)

2 *Cat and Turtle Heart* Cats and turtles were originally used almost exclusively in this investigation because the smaller hearts of these animals could be defibrillated more easily than the ventricle of the dog (Hoffman et al., 1951) In the turtle ventricle only a single dip late in the relative refractory period is to be found (Figure 36-A) Suprathreshold stimuli applied during the interval of the dip tend to elicit brief runs of extra systoles and/or fibrillation in the turtle ventricle. Figure 36-B shows the type of response considered to be *multiple firing* and the sequence of events called fibrillation. Reactions of the turtle heart such as these cannot be elicited during other periods of the cardiac cycle. In the cat ventricle single shocks applied during diastole and most phases of the refractory period will not produce multiple extrasystoles or fibrillation. As in the dog however an early and a late or major dip are found Although there is much variation in this species in susceptibility to fibrillation, it is possible to ascertain that both during the early and late or major dip areas in contrast to other intervals of the cycle the heart tends to respond by repetitive extrasystoles and/or fibrillation to shocks of suprathreshold intensity At least one dip or vulnerable period is always obtained in test

FIGURE 35. Strength interval curves (•—•) showing location of vulnerable period in the dog (A B C) and cat (D) ventricle Vulnerable period is shown by cross-hatched area In C the vulnerable period is outlined by stimuli of 1 msec. (o——o) and 10 msec. (x x) duration D—strength interval curve showing 2 dips and 2 periods of vulnerability (x——x with cross-hatching) A no response phase (o——o) separates the two vulnerable periods







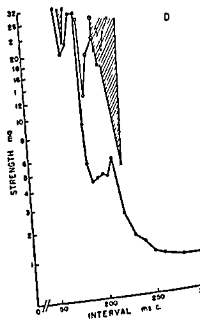


FIGURE 35 (*See legend facing page*)

ally give origin to propagated responses can more easily be created than earlier and later in the cycle. Strong suprathreshold stimuli applied in these 'dip periods create effects which eventuate in either multiple extrasystoles or fibrillation The presence of an early and late vulnerable period in at least some ventricles tested resolves the contradictory claims that the heart is vulnerable immediately after the absolute refractory period on one hand (Lovatt Evans, 1952) and the statement that vulnerability is associated with the terminal phases of repolarization (Wiggers 1949)

The possible meaning of the relationship between tendency to fibrillation and periods of incomplete and unsustained recovery of excitability will be analyzed later on after an evaluation has been made of the current ideas concerning the mechanism and nature of fibrillation

THE "NO RESPONSE PHENOMENON

If the strength of stimuli applied during this vulnerable period i e., at the time of the dips in the strength interval curve depicting recovery of excitability is still further increased above that level necessary to produce fibrillation the stimuli eventually become completely *ineffective* and produce no response which can be detected electrocardiographically or by visual examination of the heart's action This is termed the 'nothing or no-response" phenomenon Following attainment of the high intensities progressive reduction of stimulus strengths again elicits but in reverse order, the types of response which were seen as the intensity was stepwise increased i e, fibrillation, multiple and single extrasystoles are again induced by stimulus strengths within the previously observed threshold ranges (Brooks et al., 1951) This 'no response" phenomenon has been observed in both the auricle and ventricle of all species studied but is most readily obtained from the auricle The periods during which it can be elicited precede and overlie the phases of vulnerability (Figure 34-A and B 35 D 36-A) With the strength of stimuli which could be delivered by the stimulators employed a no-response phenomenon was never obtained at other periods of the cycle

Phenomena somewhat similar to this failure of very strong stimuli to produce a propagated reaction at a time when tissues are capable of being excited by weaker stimuli have been observed by others Blair and Erlanger (1933) found that if an excessively powerful test stimulus is used to measure recovery of excitability, a longer recovery interval

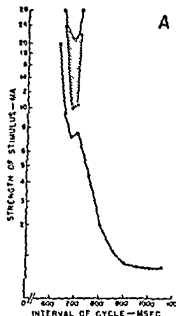


FIGURE 36 A Strength interval curve (•—•) of turtle ventricle showing thresholds for fibrillation (x——x) and no response (o——o)

B Electrograms from turtle ventricle showing the arrhythmia considered to be fibrillation (Reproduced with permission from the Amer J Physiol 1951 *167, 88*)



ing the excitability of the ventricle In cases giving an early and a late *or major dip*, vulnerability is not always detectable in both dip areas—it occurs either at one or the other but in approximately fifty per cent of the experiments on cat ventricle giving clear double dips, there are two vulnerable periods (Figure 35 D) The greatest vulnerability generally occurs within the major dip but occasionally falls slightly later in the cycle *It never occurs during* the supernormal period either in these species or in the dog

In conclusion it can be said that in both the auricle and ventricle there are phases of temporarily increased excitability *in the relative refractory* period During these phases local excitatory processes, which will eventu

waves of various amplitudes originating within the myocardium (Prinzmetal 1953) and by asynchronous contractions of minute muscle segments and a failure of the pumping action of the heart it is thought to originate as a consequence of relative differences in the physiological states of different parts of the myocardium (Garrey 1924)

In the literature pertaining to the etiology and nature of flutter and fibrillation the various theories presented tend to emphasize one or another single causal mechanism.

✓ There are two competing ideas 1) the *circus movement* concept (Garrey, 1914) somewhat oversimplified by Lewis (1918) and applied by Wiggers (1940) which postulates the irregular reentry of impulses and 2) the *ectopic focal stimulation* concept which assumes a mechanism whereby repetitive and disorganized stimulation arises either from a single focus (Rothberger and Winterberg 1914, Scherf and Terranova 1949 Prinzmetal et al. 1952) or from multiple foci (Engelmann, 1896 Kisch 1950) One is thus led to infer that fibrillation and flutter are due to the one or the other mechanism.

In flutter there is abnormal rapidity of contractions but regularity of action is maintained as though the organ or chamber were still under the control of an organized pacemaker or a group of pacemakers with identical rhythms In irregular flutter and fibrillation activity is even more continuous but in this instance an irregularity of action of heart elements is perceived. It is difficult to conceive of regularity without a dominant pacemaker and confined pathways of transmission It is also difficult to think of irregularity in terms of multiple pacemakers with fixed loci or in terms of a movement of excitation uniform enough to permit use of the term circuit. Obviously numerous phenomena must be dealt with by any explanation of fibrillation and flutter which is advanced

The circus movement and reentry theory has many supporters despite recent strong attacks upon it (Prinzmetal et al. 1952) and no definite choice of any one mechanism of flutter and fibrillation has as yet been universally accepted (Hecht, Katz, et al. 1953) The present situation may be summarized much as follows

CIRCUS MOVEMENT THEORY Circus movement could be of two types

1) A regular circuit of travel by the excitatory impulse with reentry occurring in a narrowly confined specific pathway As the wave of excitation journeys in this circuit, impulses emanate from it in a regular

is indicated than if less strong currents are used Fitzhugh (1954) has also observed that above an optimal intensity test stimuli are less able to stimulate a nerve early in its recovery phase—the stronger stimuli have no effect at a time when weaker stimuli will induce a propagated response

In discussing the "no response" phenomenon two problems must be considered 1) why strong stimuli produce no effect when weaker suprathreshold ones will do so at the same intervals of the cycle and 2) why there is a drop in threshold for this phenomenon at the "dip" area of the cycle Hypotheses which can be offered in explanation of these two observations are as follows It seems reasonable to assume that the rise of the current to high intensities must actually stop normal reactions which start as the current is rising to the high value, either locally or in some areas a little removed from the electrode

It is well known that anodal polarization at one electrode can be made strong enough to block propagation of an impulse down a nerve from the region of the cathode (Fick, 1863, Lorente de No, 1947) Biedermann (1885) long ago reported the production in heart muscle of a propagated relaxation traveling from the anode following application of strong current flow Weidmann (1951) has shown a similar phenomenon—propagated repolarization in the isolated Purkinje fiber It is conceivable that when the "no response" phenomen is elicited in the heart, the anodal current flow may actually have a predominating action and not only repolarize but actually hyperpolarize the cells momentarily causing an anodal block to all excitatory effects from the cathode Such strong stimuli do not have an irreversible action and appear not to be injurious

It is known that this "no response" phenomenon can be elicited in isolated irritable tissues of the heart but it has not been produced in fully repolarized non refractory muscles of the heart The phenomenon is therefore dependent upon conditions prevailing in heart cells at a particular phase of the cardiac cycle Further study of this phenomen is certainly required

THE NATURE OF FIBRILLATION AND EXPLANATIONS OF ITS ORIGINS

Fibrillation is a state of incoordinated activity of the myocardium It is identified electrocardiographically by the presence of heterorhythmic

waves of various amplitudes originating within the myocardium (Prinzmetal 1953) and by asynchronous contractions of minute muscle segments and a failure of the pumping action of the heart, it is thought to originate as a consequence of relative differences in the physiological states of different parts of the myocardium (Garrey 1924)

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1) A regular circuit of travel by the excitatory impulse with reentry occurring in a narrowly confined specific pathway As the wave of excitation journeys in this circuit, impulses emanate from it in a regular

sequence Such a concept requires that this primary pathway be pro tected from all intrinsic excitatory impingements other than that of th one traveling impulse

This theory had origin in the observation of Mayer (1908) that if wave is started in *only one direction* in the ring of muscular tissue in th mantle of a jellyfish, it travels for a relatively long time Mines (1913) and Garrey (1914) found that the same phenomenon would occur unde certain conditions in rings of atrial and ventricular muscle of the hear and used this observation as a basis for explaining the continuous activity of flutter and fibrillation Thomas Lewis (1918) carried this idea a step further and suggested that in auricular flutter a circus movement is se up which travels continuously round a ring of auricular tissue, namely a ring of auricular tissue surrounding the junctions of the inferior and superior venae cavae (see also Rosenblueth, 1953) As the wave travels about this ring the excitatory process spreads out to activate other parts of the auricle

A favorable anatomic situation such as a shorter path or more for tuitously arranged bundles of parallel fibers could permit a confined and faster circuit of transmission in certain areas of the heart A lateral spread of impulses could occur but these would be confined a) by the following refractoriness in the primary circuit channel, b) by the activity from an earlier excrescence of activity and c) by the fact that the faster traveling impulse in the primary circuit would always start other laterally moving impulses ahead of earlier ones Thus there would be confined channels of spread and movement but also an appearance of wave motion (Figure 37 A) This scheme of things would give regularity, would permit a wave like movement and would protect the original circus channel

2) Circus movement could be random and not confined to any ana tomical or physiologically determined pathway It might be a more meandering type of movement reflected from refractory tissue and turn ing always in the direction of responsive tissue it would eventually reinvade or reenter tissue it had excited before Such a wave front could divide repeatedly as the heart action became progressively more and more disorganized It has been observed that when the tissue mass is small ex tinction is likely to occur and spontaneous recovery results This could be the reason why smaller hearts cannot be easily caused to fibrillate while larger hearts fibrillate readily and rarely recover It would also

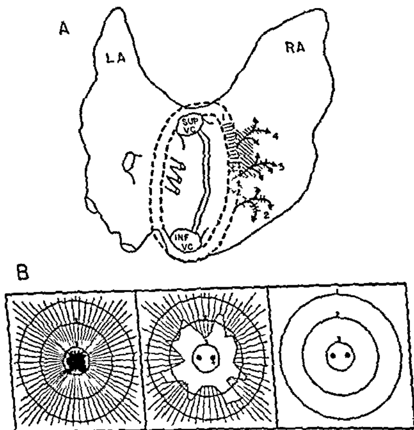


FIGURE 37 Diagram of circus movement showing major circuit (1) the origin of subsidiary circuits (2, 3 4) and possibility of reentry

B Diagrams of post-excitation recovery of the auricle and the mechanism whereby stimuli of various strengths might *produce* extrasystoles, fibrillation or the no-response phenomenon Explanation in text. (Reproduced with permission from the Amer J Physiol., 1950 *16?* 219)

explain the frequent observation that any influence which diminishes conduction velocity and the duration of the refractory period tends to set up arrhythmias

Slowly conducted waves of a repetitive nature have been observed in auricular flutter (Rosenblueth and Garcia Ramos 1947 a and b Wiener and Rosenblueth 1946) and electrical recordings have confirmed the

presence of circus activity (Cabrera and Sodi Pallares, 1947) In accounting for the phases of fibrillation the early undulatory stages have been explained on the basis of slow waves spreading out over the total surface and reentering near the focus of stimulation These break up into smaller and smaller circuits as a state of greater incoordination is reached and finally there are innumerable groups of contracting fibers whose action can hardly be described in terms of circuits (Wiggers, 1940 Fig 2, p 406) Even when direct recording by means of contiguous punctate electrodes, 1 mm or less apart, is used, it is found that during fibrillation there is no fixed sequence of events even within the very localized area under these electrodes This indicates that the fragmentation is very great

THE ECTOPIC FOCUS THEORY There are also variations of this concept

1) *The theory of a single ectopic focus* The production of rapid auricular arrhythmias by circumscribed applications of certain drugs (Scherf, 1947) and the possibility of arresting the arrhythmias (at least of tachysystole and flutter) by removal or cooling of the initiating focus has prompted the revival of the theory of focal origin of flutter and fibrillation Furthermore, recent high speed cinematographic studies (2000 frames per minute) have been interpreted (Prinzmetal, 1953) as showing no indication of circus movement in auricular and ventricular flutter and fibrillation Moderately irregular contractions at a rate of 400 600 per minute, and faster, smaller, more irregular contractions (800-1600 per minute), are seen to occur in muscular elements during these conditions Those adhering to this concept believe that "fibrillation originates from and is perpetuated by a single ectopic focus" giving an over rapid origin of beat (Prinzmetal et al, 1952)

2) Other cardiologists (see Katz and Pick, 1953) believe that in fibrillation multiple ectopic foci of beat origin arise and fragment the heart into numerous small independently acting units It is true that to the observer of ventricular and auricular fibrillation an independence of action of muscular elements at certain stages is more apparent than circus movement Furthermore since each fiber of the heart is potentially an autonomous pacemaker or at least possesses the ability to develop an intrinsic rhythmicity of action unless dominated by a more rapidly firing tissue, it seems reasonable to assume that multiple ectopic foci of beat origin could develop

To consider that multiple independently acting pacemakers could have a sufficiently uniform intrinsic rhythm to produce slower regular ar rhythmias might call for a stretch of the imagination but certainly this theory presents less difficulties when one endeavors to account for the fragmentary and irregular activity of fibrillation

3) There are other variants of this view The concept of multiple self-sustained microsystole (Wenckebach and Winterberg 1927) is fre quently mentioned It is also thought that repetitive firing may result from a single "sink" or area of depolarization created by injury or local application of a drug A local excitatory state created by a single stimulus will produce fibrillation or multiple systoles after a latency if the stimulus is applied during the vulnerable period (Brooks et al., 1951, Hoffman et al 1951)

These several theories have received strong support but no unanimity of opinion prevails In view of this disagreement and the fact that current theories do not take into account certain factors of major importance, an additional concept is offered

A CONCEPT OF THE ROLE OF ELECTROTONIC CURRENT FLOW IN THE PRODUCTION AND MAINTENANCE OF FIBRILLATION

The origin of fibrillation is most readily explained by the assumption that the provocative agent creates an inequal effect on the tissues of the heart. Local application of cold creates an assymmetry in that activity is initiated in normal and cooled tissue. Local application of drugs local injury or localized anoxia creates a similar situation The application of electric current during the relative refractory period also produces a degree of assymmetry in that under the anode repolarization and under the cathode depolarization is effected. This aggravates the possibility of uneven recovery and a differential effect of the excitation Development of fibrillation likewise requires an asymmetric propagation of excitation All of the known fibrillation producing agents which have been described act initially by producing some local dissymmetry in some aspect of excitability The major problem is how this asymmetry becomes general ized. This conceivably might be explained by uneven progression of ac tivity resulting in reentry and disorganization.

Any active area or depolarized region of cell membrane gives rise to electrotonic currents because of the sink source relationships created (Chapter II) This current spreads through all adjacent conducting media and if sufficiently concentrated will excite tissues through which it passes This is the normal process of propagation of an impulse

It can be presumed that because of anatomical and other reasons the cells in any area are not equally exposed to such currents Moreover, under conditions where heterogeneous states of excitability maintain, as during recovery of excitability, the possibility of a non uniformity of response is exaggerated Thus certain cells will respond to a nearby focus of activity before neighboring cells which may be closer to the already depolarized "sink" area These sensitive cells will fire and stimulate their neighbors Thus a type of "saltatory conduction" may transport excitation from one point of sensitivity or greater instability to another, initiating new foci of activity in a progressive but random fashion Because of their earlier activation these initially excited cells will also recover sooner than will their neighbors which were later aroused to activity Saltatory conduction of excitation could produce activity in cells with substantially different phase relationships in an area which would become greater and greater Any specific area could be invaded and reinvaded from any adjacent but not necessarily contiguous area of the myocardium Any impairment of conduction would of necessity accentuate phase differences in activity and favor a saltatory progression of the excitatory process along anatomical pathways

The only difference between this concept and that of the normal progression of a depolarization wavefront is the action of a saltatory conduction mechanism, the steps of which are determined by the presence of scattered sensitive points which can be readily touched off by spreading electrotonic current flow Any buildup of intrinsic excitation or instability would make cells susceptible to the eddy currents emanating from activity elsewhere and would trigger their depolarization prematurely This saltatory conduction would depend upon variations in the state of irritability and the impulse would jump from one local point to another by a pattern determined entirely by rates of recovery from previous excitation and by proximity to activity in adjacent tissue

It is difficult to comprehend how such a mechanism as this could be eliminated from consideration It is also difficult to see how such a phenomenon could be proved to occur but it is known that electrotonic currents do excite, that they do accelerate activity in pacemakers (McWilliam, 1888a) and that on the anodal side they aid in repolarization (Weidmann, 1951) Electrotonic currents spread out from every depolarized area of living tissue, they promote conduction and cause excitation, they can affect distant tissues and cause transmission across an inactive

barrier It is reasonable to assume they could touch off activity in a cell somewhat distant from the border of a stationary or an advancing sink.

In summary, circus movement and the conventional type of reentry seem to account for many of the observed phenomena in a quite adequate fashion Moreover independently acting ectopic pacemakers are known to develop in the heart. On the other hand it is difficult to explain all phenomena by a simple circus movement theory It is also difficult to accept the idea that a series of completely independent pacemakers, each dominating its quota of fibers without being affected by activity in adjacent tissue, can produce all the phenomena observed to occur in studies of flutter and fibrillation In fibrillation particularly it seems most reasonable to think that an individual cell may escape from domination and either aided or unaided initiate a localized excitation and also that such a cell may be excited by one pacemaker at one time and by a spread of activity from a different pacemaker at another time The possibility of electrotonic current effect and saltatory spread of activity from point to point should not be disregarded

PRODUCTION AND NATURE OF FIBRILLATION

The nature of fibrillation and the vulnerability of the heart to the production of fibrillation by electrical stimuli have been discussed but little has thus far been said concerning possible causes of vulnerability or concerning the development of these abnormal states of cardiac activity Fibrillation can be produced by so many means that one immediately questions the existence of one common causal circumstance More will be said about this as the action of drugs ions temperature changes, etc., on the excitability of the heart are discussed but first it must be recognized that three rather distinct problems must be dealt with They are 1) conditions initiating fibrillation 2) the cause of vulnerability to fibrillation at particular periods of the cycle and 3) the requirement for certain strengths of stimulation to initiate fibrillation during these periods of vulnerability

It should also be recognized that fibrillation develops in a progressive manner It begins from a local disturbance but eventually envelops the whole auricle or ventricle It originates from a series of rapid beats which at first have the appearance of almost normal extrasystoles An explanation of the multiple firing is thus required as well as an explanation of the progression to disorganized activity

CONDITIONS AT ONSET OF FIBRILLATION In preliminary analysis it can be said that fibrillation basically is a disorganized activity of the components of cardiac muscle No single predisposing factor is invariably associated with origin of this type of arrhythmia For example

1) An acceleration of the heart rate beyond the ability of all elements to follow can disorganize the heart action and cause fibrillation

2) A localized excitation or arousal of ectopic pacemakers can disorganize the normal sequence of events and cause the heart to escape from any specific pacemaker dominance and thus fibrillate

3) Failure of or abnormal slowness of conduction may permit potential subsidiary pacemakers to escape from dominance or may permit locally acting excitatory conditions to become effective and thus disorganize heart action A localized slowing of conduction in a cooled or partially depressed area will permit reentry of an impulse into surrounding areas (Hoff and Stansfield, 1949)

4) Disproportionate changes in conduction and pacemaker action may accomplish the same end Accelerated intrinsic excitation may permit escape even though conduction from the normal pacemaker remains normal

5) Either abnormal shortening or lengthening of the refractory period can result in fibrillation, especially if these changes are disproportionate in the various cardiac cells

6) Differential changes in the excitability of cells can cause fibrillation

A somewhat different analysis of the conditions or factors causing the onset of fibrillation is the following An initiating force or condition may act extrinsically or intrinsically Extrinsic stimuli of a mechanical, thermal, chemical or electrical nature may initiate fibrillation, particularly if favored by intrinsic conditions causing reentrant impulses, disorganized conduction and regional blocks Enhancement of depolarization by toxic focally acting drugs (aconite) or by an infarct and/or enhancement of excitation by electrotonic currents may initiate disorganized activity

The production of multiple extrasystoles by a strong shock can be explained on the basis of multiple discharges from a long lasting "sink" or depolarized area of the membrane (Chapter 2) Similarly, local areas of injury and areas which are differently polarized due to action of drugs, current flow, cooling, etc, do set up a current of injury This current flow could be responsible for repetitive firing from such a locus if the adjacent membrane is sensitive and also possesses an ability to repolar

ize up to the boundary of the persisting injury or depolarized areas. Production of fibrillation by strong electrical shocks does involve the creation of local areas of excitation This is indicated by the long latency of response to stimuli applied during the subnormal phase of the cycle Additional evidence that a long lasting local excitatory state can be created by an applied stimulus is that in testing cardiac excitability, constant thresholds are found only when test stimuli are applied at well spaced intervals The effects of a testing stimulus do not completely disappear for two or more cycles (Chapter III) and furthermore, the after-effects of such a stimulus may summate with activity of a pacemaker enabling it to escape from an imposed rhythm (Orias et al., 1950a)

Thus any area of injury or persisting depolarization not only acts as a block to conduction but can also serve as an initiator of repetitive excitation since it gives origin to a constant flow of current which may have an effective excitatory action. It has been shown that when "polarized states are created in the ventricle by continuous cathodal and anodal current the repetitive activity resulting does not have one exact locus of origin (Harris and Moe 1942) Finally the progressive shortening of refractory periods as the rate of extrasystole production increases also conceivably contributes to the development of disorganized activity and fibrillation

THE NATURE OF VULNERABILITY The vulnerable period is associated with the relative refractory period and greatest vulnerability is coincident with the "dip in the excitability recovery curve The nature and origin of this dip has been discussed (Chapter V) The period of the dip is a time during which the heart is more susceptible to stimulation than it is just before and just after it is a period during which multiple extrasystoles, fibrillation and the *no-response*' phenomenon can be evoked

During the refractory period the local excitatory state created in the region contiguous to the testing electrode does not immediately produce a normally propagated response The eddy currents emanating from the persisting localized sink may create an asymmetry of propagation and reentry because of an asynchronous recovery of surrounding fibers associated with a continued electrotonic current flow due to persistence of the localized sink or excitatory foci Repetitive firing may result from such constant current flow and it is common knowledge that fibrillation eventuates from a series of extrasystoles

Another contributory factor is that the action potential produced by *this stimulus*, because of the incomplete repolarization, will be of small amplitude and consequently will propogate slowly and with a lower *safety factor* The decreased stimulating efficacy of this small action potential might exaggerate any normally present asynchrony of the repolarization process Thus excitation would occur later in some cells than in others because they had lagged slightly behind in their repolarization A wave of excitation is thus visualized as passing down certain fibers permitting others to fire later by a process of reentry This development of asymmetry of response is conceivably favored by the anodal and cathodal effects of the stimulus mentioned previously The crucial requirement for fibrillation resulting from either of these causes is the possibility that some fibers are able to conduct at a time when others are not

Coincidence of vulnerability with the dip may occur because 1) long lasting excitatory states are more easily created in the dip period than later in the cycle and 2) uniform progression and termination of activity is interfered with by the regression of excitability that follows the dip This effect conceivably results in repetitive or fragmentary discharges and fibrillation

It is generally stated that the vulnerability to fibrillation occurring toward the end of the refractory period is due to the fact that certain fibers have recovered normal excitability before others For example, it has been suggested that the dip and presumably vulnerability of the ventricle is due to temporal separation of the recovery process in muscle and Purkinje tissue (Moe et al, 1955) This is a possibility but one might expect, on the basis of such an hypothesis, to find the heart vulnerable until well after completion of recovery in the ventricular muscle because repolarization of the Purkinje fiber is very slow (see Chapter V) This supposition does not explain the localization of vulnerability early in the relative refractory period or the dip and vulnerable period in the auricles Finally, another possible factor in the production of fibrillation at these phases in the cycle is this Extra beats occurring immediately after repolarization show a very swift repolarization and a very brief refractory or irresponsive period This would favor rapid repetitive firing from a persisting localized sink or excitatory process and could conceivably contribute to the establishment of ectopic pacemakers or to the disorganization of normal rhythmic responses to a pacemaker drive

RELATION OF THE STRENGTH OF STIMULATION TO THE PRODUCTION OF FIBRILLATION Graded strengths of stimuli when

applied during the vulnerable period produce 1) extrasystoles, 2) fibrillation and 3) the "no-response" phenomenon

The type of response may be assumed to depend upon the conditions of excitability of the fibers under and in the immediate vicinity of the electrodes and upon the extension of the potential field created at the site of stimulation when the shock is delivered If a shock is applied during the absolute refractory period, there will be no response within the usual strengths of stimuli employed (Figure 37 A, Orias et al 1950-a), indicating that any local excitatory state or persisting "sink" created by the stimulus is in such case unable to outlive the refractory period of the muscle With respect to the relative refractory period a stimulus applied during this phase of the excitability cycle will initiate a response if it creates an excitatory process which can persist until repolarization has been completed and propagation can occur Following complete recovery of normal excitability stimuli of any suprathreshold strengths produce only extrasystoles (Figure 37 C) During the vulnerable *period* however three types of response are obtainable. The assumption can be made that the process of recovery starting at the place where activation *is first produced* progresses as a wave requiring a certain time to reach the more remote parts of the auricular or ventricular muscle. In Figure 37 B the white area in the center represents the fibers that have recovered *some excitability* the shaded area represents fibers which are still completely refractory and the irregular boundary between them represents the progress of the wave of recovery at a particular instant. This progress is represented by an irregular line in accordance with the thesis that recovery itself does not proceed at precisely identical rates in all subdivisions of the myocardium It is reasonable to assume that the fibers which have attained a degree of relative refractoriness are also not in identical states of recovery

A stimulus which is relatively weak, but is nevertheless strong enough to produce an extrasystole may be assumed to do so because it creates only in the region of recovery a potential field of sufficient strength to initiate an impulse (Figure 37 B circle 3) There results a propagated wave of excitation which sweeps over the myocardium in the wake of the retreating *border of absolute* refractoriness and this is recorded as an extrasystole

A stronger stimulus is assumed to create a similar but larger field which now extends in effectiveness to the irregular boundary of recovery (Figure 37 B circle 2), thereby overlapping adjacent strips of tissue,

some of which have recovered and others of which are still refractory In this circumstance certain fibers are stimulated and certain others are not and it might appear that several isolated foci of beat origin are thus created which might give rise to reentry and disorganization of myocardial elements thereby leading to fibrillation

With a still stronger stimulus, the effective field would extend to completely refractory areas (Figure 37 B, Circle 1) and would therefore produce no propagated response It is assumed in this latter case that those areas of the myocardium which have recovered some ability to respond are activated but produce no electrical or mechanical event recordable by the means employed The "nothing" phenomenon, therefore, is due to the fact that a very strong stimulus redepolarizes the total recovered area or polarizes it in such a manner as to permit no extrasystole to propagate It seems more probable, however, that the very strong stimulus itself creates a hyperpolarization or some condition which blocks propagation



DISCUSSION AND SUMMARY

In concluding this discussion of fibrillation, certain concepts should be given special emphasis

1 The heart is comprised of potentially autonomous elements which contract in a uniform sequence because their activity is dominated by the excitatory action of a pacemaker, the sinoauricular node, which is that portion of the heart tissue possessing the highest intrinsic rhythmicity of action Abnormal occurrences or states may interfere with this dominance thereby permitting origin of excitation in one or more ectopic foci

2 Normally the excitatory process spreads outward from this pacemaker over nonspecialized and specialized conducting tissues in such a fashion as to evoke a sequence of events favorable to the pumping action of the heart. Conduction can occur, however, in practically all directions within the heart due to the syncytial nature of cardiac muscle Consequently excitation originating in ectopic foci may evoke an abnormal sequence of events or so interfere with the spread of impulses from the normal pacemaker that activity of the heart becomes disorganized This property of multidirectional conductivity provides a second potentiality contributory to disorganization of effective cardiac pumping action

3 Fibrillation is a state of disorganized activity of cardiac muscle elements It usually develops progressively rather than instantaneously

from the action of disorganizing influences or situations although this progressive fragmentation of activity may require only a few seconds

4 Once disorganization has occurred the potential automaticity of cardiac muscle units and the syncytial nature of the myocardium, which enables it to serve as a homogeneous conductor permits reentry of activity and creates such a constancy of excitation and response that no pacemaker can regain dominance

5 Circus movement, activity of ectopic foci, and the excitatory action of electrotonic current flow can and in all probability do contribute to the origin and maintenance of fibrillation Both the disorganizing action of reentry, and the origin of activity at ectopic sites from a combination of intrinsic and imposed excitatory forces can be said to maintain the fibrillatory state The mass of tissue available to sustain this continuous activity is a factor also smaller hearts being more readily dominated by a pacemaker

6 Fibrillation can originate from many primary causes. a) A non uniformity of refractoriness and recovery from activity can establish an asymmetrical condition leading to disorganization of activity and fibrillation For example a progressive acceleration and tachycardia does not produce fibrillation until some elements or areas of the muscle are unable to follow the driving rate Due to a longer or a less rapidly shortening refractory period they eventually are not able to respond to the initial stimulus and are secondarily activated out of phase with the other elements This out of phase activity provides a means of reentry and disorganization of heart action b) Asymmetry of conduction can also lead to disorganization Potassium chloride certain fibrillatory drugs cooling and artificial block act in producing fibrillation by interfering with conduction c) Excitability changes and changes in intrinsic excitatory processes can lead to disorganization Electrotonic current flow originating from localized areas of injury or the localized excitatory action of a drug like aconitine can by aiding in the establishment of ectopic foci of impulse origin produce fibrillation

7 It is not the direction of change which leads to disorganization but the fact that changes in refractoriness conduction and excitability are not uniform or universal within heart elements The direction of the change is relatively unimportant because factors which prolong refractoriness can produce fibrillation while other factors which shorten refractoriness can lead to the same end result. Acceleration of conduction

as well as slowing will cause fibrillation if the change is not uniform throughout the heart Locally acting excitatory and locally acting depressor influences will both lead to fibrillation Thus it is not the change in itself but the relative change 1) in various parts of the myocardium or 2) in various parameters of myocardial properties which lead to fibrillation In this latter case changes in the intrinsic excitatory process, recovery from refractoriness, and conduction which are in opposite directions or which occur to degrees which are not equivalent, promote disorganization

8 The heart is vulnerable to fibrillation by electrical shock only during its relative refractory period It is most vulnerable at certain particular intervals of this period However, fibrillation does not originate in the refractory period nor directly from the applied shock which leads to the establishment of this arrhythmia During the refractory period the heart tissues undergo a phase of rapid change and are in a less uniform state Imposed shocks tend to aggravate this dissimilarity, for example, by delayed excitatory action on some fibers and not on others Properties of refractoriness, ability to conduct excitation, and to originate and respond to excitation are least similar in different cardiac elements during the refractory or irresponsive period

9 The greatest vulnerability occurs in the "dip" areas of the refractory period because it is then that thresholds are lower and because it appears that events within the heart are not progressing in as uniform a fashion as at other intervals of the refractory period There is thus a greater possibility not only of a stimulus having an effect but also that fibers of the heart may be affected to dissimilar degrees The vulnerable periods (dip areas) are intervals during which anodal current flow is more effective and the action of such current apparently is that of aiding the repolarization process This conceivably would increase dissimilarity of states in the myocardium, some elements adjacent to the anode being restored to normal excitability while adjacent cells remain partially depolarized The potentiality for disorganization of activity under such conditions is obvious

10 Disorganization once having resulted in fibrillation, action of the heart as a pump ceases This situation can be terminated only by bringing cells into step again and under the domination of a pacemaker This will occur, if due to a limited mass of myocardium available, fibrillatory activity is self terminating, or if the periodicity of activity of cells can

be forcibly brought into phase again This latter can be accomplished by the action of cold KCl and countershock all of which stop all activity for a sufficient period to permit the pacemaker to assert its more rapid intrinsic processes of excitation and once more assume its dominating role (see Chapter IX)

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VII Cardiac Reactions to Heat and Cold

This is a discussion of the reactions of the heart which are involved in the compensatory responses resulting from exposure of the body to heat and cold It deals also with the effects of heating and cooling the heart itself or its component tissues on excitability conduction, recovery from refractoriness the transmembrane potential and the contractile process.

EXPOSURE OF MAN AND OTHER MAMMALS to extremes of temperature has marked effects upon the heart long before the heart temperature or the temperature of the body as a whole is modified to a perceptible degree. It is well known that shivering and the increased muscular and metabolic activity required to maintain body temperature on exposure to cold impose a considerable augmentation of work load on the heart. A similar increase in cardiac activity is also required to maintain sufficient heat loss from body surfaces during exposure to high environmental temperatures It has been found that as a result of such demands individuals with a degree of congestive heart failure have a low tolerance for temperature change There is a higher incidence of death from cardiac cause during heat waves or in a hot, moist climate (Shattuck and Hilferty, 1933 Newburgh 1949 Berenson and Burch 1952 Ferrer 1952 Heyer et al. 1953) The interest of physiologists and physicians however has not been confined to the consequence of commonly encountered mild degrees of stress The use of hypothermia and hyperthermia in medical treatment has had its vogue and at present there is renewed interest in hypothermia as an adjunct to cardiac surgery (Bailey et al 1954 Swan and Zeavin, 1954) Military operations during the last decade have also necessitated a study of cold injury and the tolerance of the body for extremes of temperature

An adequate consideration of the effects of temperature on cardiac activity involves a study of the changes produced by neural and humoral agents which regulate cardiac activity and the consequences of cooling and heating the heart itself These indirect and direct actions of heat

and cold on excitability and responses of the heart will be reviewed in this chapter

INDIRECT EFFECTS OF HEAT AND COLD ON HEART ACTION

There have been numerous summaries of the body reactions which maintain a constancy of the internal environment despite the stresses imposed by fluctuating external environmental circumstances (Cannon, 1932, Selye, 1950, Horvath, 1951) The compensatory adjustments are of two types 1) those which provide immediate but somewhat temporary compensation and 2) those which are of the nature of long term adjustments essential to the establishment of new equilibria The latter type of response is an adaptation or in the case of adjustment to environmental temperature changes an acclimatization Changes in cardiac activity are frequently demanded by compensatory reactions and often are of considerable magnitude On sudden exposure to the low oxygen pressure of high altitudes cardiac output rises This is an immediate compensatory reaction but the heart is also involved in permanent adaptation in that it maintains a high output in those individuals who live permanently at high altitudes and may even show some enlargement (Dill, 1938, Monge, 1948, Van Liere, 1942) In the case of stress created by temperature change the cardiac reactions evoked are of the first category only in that they are immediate but diminish as adaptation to heat and cold occur There is no evidence that man living in the far north has a permanently higher metabolism, cardiac output or a larger heart size than normal It is well known that exposure to cold sets up a very complicated series of interrelated reactions which preserve the normal body temperature by increasing heat production and conserving that which is produced These compensatory reactions are initially touched off by afferent impulses from receptor organs in the skin, the end bulbs of Kraus, which are stimulated by a temperature fall of 0 004° per sec for one second (Hardy and Oppel, 1938, Scott and Bazett, 1941 Granit, 1955) If cooled blood reaches the hypothalamus there is a reinforcement of these reactions but this mechanism of activating the compensatory responses is less sensitive and a fall of at least 0 2° to 0 5° C in blood temperature is necessary to evoke this reaction The posterior hypothalamic regions are essential to the integration of effective body responses to cold (DuBois, 1948, Fulton, 1955, Gillilan, 1954)

Similarly, exposure to heat stimulates heat sensitive receptors (Ruffini

endings) in the skin These sensory elements require a temperature change of approximately 0 001° C. per second for at least 3 seconds for their activation External temperatures must be at least 45° C. or over to create the required heat gradient in body surfaces at normal body temperatures (DuBois 1948 Grant, 1955) These endings adapt very quickly and for this reason reflex responses to heat tend to be of short duration. Chemoreceptors within the carotid and aortic bodies are also affected by hyperthermia and cause a reflex acceleration of the heart (Aviado and Schmidt, 1955) Warming of the blood flowing to the head of an animal likewise causes compensatory responses which favor heat loss even though skin temperatures are normal. In this case the anterior hypothalamus and preoptic areas of the brain are responsible for the integration of compensatory adjustments (Magoun et al 1938 Brooks 1948 Fulton 1949) There are species differences in the dependence on central and peripheral receptor mechanisms (Brooks, 1948) Even though their body temperatures are normal, dogs can be caused to pant by warming small areas of their skin but birds are more dependent upon blood temperature changes. Man and most mammals depend upon both types of stimuli.

The heart is affected both by the body reactions which favor heat dissipation and by those which produce and conserve more heat. These cardiac responses are initiated by reflexes by the action of humorally transported agents and by the direct action of heat and cold on the heart as warm or cold blood reaches that organ. In many conditions of extreme stress the action of the heart is determined by directly as well as indirectly acting influences and this must be kept in mind when analyzing the responses to heat and cold.

CARDIAC REACTIONS RESULTING FROM EXPOSURE OF THE BODY TO HIGH TEMPERATURES The stresses imposed on man and other animals in a hot climate are amply described by Dill (1938) and Newburgh and his associate (1949) The physiological adaptations required for survival are also well known (Walsin, p 3, Herrington, p 262, see Newburgh 1949) It has been estimated (Adolph, 1938) that 2.5 liters of blood per minute must be circulated through the skin to dissipate the heat produced by walking in the desert. Another somewhat bizarre estimation of this increase has been the finding that at 40 C. ten per cent of the cardiac output of an African monkey goes through its tail (Hongo and Luck, 1953) This is about 60 per cent rise above the volume flow at normal temperatures. This increased blood flow through

dilated peripheral vessels requires an increase in cardiac output. Heart rate and cardiac output *do rise when the body is exposed to heat* (Scott et al, 1910) The increase in cardiac output at rest produced by heat (40° C) is 1 3 liters, or an increase of 31 per cent above the basal output at thermal neutrality which in the instance quoted was 4 2 liters During hard work under cool conditions cardiac output rises to 18 9 liters but in a hot environment there is an additional rise of 11 per cent or 1 7 liters when the same work is undertaken

Much greater percentage changes occur in heart rate due to heat stress This increase in rate is progressive (Clark, 1927) and appears to be graded in proportion to the stress (Herrington, 1949) It has been found that the average pulse rate for reclining men at normal temperature is *74 beats per minute (Schneider, 1941) After exposure to a temperature* of 41° C for a few hours the average rate is 120 although body temperature does not rise significantly If subjects merely sit upright instead of recline, the average pulse rate is 140 at 41° C When man carries on mild exercise in the heat, the average heart rate is 180 beats per minute and this represents the approximate upper limit of tolerance Voluntary tolerance of work under hot conditions is related to the degree of acceleration of the heart (Craig et al, 1954) When body temperature begins to rise, a further acceleration occurs Haldane (1905) claimed that the increase in heart rate is about 20 beats per 1° F or 36 beats per 1° C rise in body temperature More recently (Tanner, 1951) has stated that there is an approximately linear relationship between body temperature and heart rate and that there is a rise of 11 to 12 beats per 1° F rise in oral temperature in fever

The response of the heart to exercise in heat has been employed as an index of physical fitness (Noltie, 1954) One of the most characteristic signs of failure of heat tolerance and the beginning of collapse is a marked acceleration of the heart (Wiggers and Orias, 1932, Adolph, 1938, Newburgh, 1949, Kanter, 1955) Failure of compensation results in a decrease in venous return, a drop in auricular pressure, a reduction in cardiac output despite cardiac acceleration, an eventual precipitous fall in blood pressure, hemoconcentration, a reduction in blood volume and an irregular heart rate (Wiggers and Orias, 1932 Daily and Harrison, 1948, Prec et al, 1949)

The cardiac responses described are due initially to autonomic reactions mediated by control centers in the cerebral cortex (Pinkston et al,

1934) and hypothalamus (Magoun et al., 1938) and reflex centers in the medulla The decrease in blood pressure which tends to result from peripheral dilatation presumably diminishes discharge of barostatic re ceptors with consequent reduction of vagal inhibition of the heart, simul taneously an augmented tonic activity of accelerator nerves is permitted (Heymans 1950) There is also evidence of direct reflex action on the cardiovascular system from peripheral skin receptors (Bazett, 1949, Gil lilan 1954) and when the temperature of the blood begins to rise this affects the rhythm of the pacemaker directly (Eyster and Meek, 1921, Scott and Reed 1951)

CARDIAC REACTIONS FOLLOWING EXPOSURE OF THE BODY TO COLD A change in cardiac activity cannot be considered either a heat producing or a heat conserving response but it is an essential com ponent of body adjustment. The increase in general body activity and the shivering which do produce more heat require that muscles must receive *more* blood (Newburgh 1949) The increase in metabolism observed when man and other animals are exposed to low temperatures indicates that more oxygen and more energy yielding materials must be transported by the blood (Ring 1936 Spealman 1949 Krog et al. 1955)

This response of the heart appears to be insured by *at least three* mechanisms It is claimed that reflex responses of the heart can be evoked directly from peripheral receptors When the skin is cooled there is an immediate cardiac acceleration (Frank et al 1954 Steinhaus 1953) It is certainly well recognized that muscular activity is accompanied by a reflex excitation of the heart and a cardiac acceleration is one of the responses evoked by the hypothalamic integration of somatic and au tonomic reactions which preserve a normality of body temperature. Even the denervated heart is caused to accelerate when the surface of the body is cooled or when a heat debt is established by drinking ice water This is due to release of epinephrine from the adrenal medulla (Cannon 1932)

Cardiac output rises on exposure of the body to moderately low tem peratures which do not change the temperature of the heart itself (New burgh 1949 Hegnauer and D Amato 1954) The increase in rate asso ciated with an augmented venous return resulting from activity is respons ible for this rather than a direct action of cold on the organ which as will be shown later, actually reduces cardiac output. As stated previously, the effects on the heart of cold are determined by a mixture of reflex

actions and direct effect of temperature on the heart (Hegnauer *et al.*, 1950)

TOLERANCE OF EXTREMES OF TEMPERATURE AND ACCLIMATIZATION Man's tolerance for extremes of heat and cold is very great when these are expressed in terms of environmental temperatures at which man can survive He can live in the polar regions and in any other part of the globe if properly protected Men can survive continuous flow of dry air at 201° F (94° C) for a few hours, clothed men can withstand quiet air temperatures of 123° F (50 5° C) for over an hour and 137° F (58 3° C.) for 30 minutes There are limits, however, and at wet bulb temperatures of 94° F (34 4° C) individuals can tolerate mild work for less than an hour, after which body temperature rises to 103° F or higher and symptoms of collapse appear (DuBois, 1948) Similarly, few men were able during the last war to survive immersion in the waters of the North Sea (4° C) for more than 20 to 30 minutes

When tolerance is expressed in terms of body temperature limits are much more circumscribed The limit for overheating is +6° C above normal body temperature and that for cooling is —12° C Nothing much can be done to increase the upper limit of survival but by using artificial respiration, blood oxygenators and perfusion pumps and proper techniques of rewarming, hibernating animals will recover from cooling to 0° C (Crismon and Elliott, 1947) and dogs, cats and man can be revived after reduction of their body temperatures to 18° or 20° C and in special cases dogs have recovered after cooling to 4° C (Gollan, 1954) Adaptation does not improve tolerance of the extremely high and the extremely low body temperatures just mentioned but there is definite evidence of acclimatization or the development of resistance to environmental heat and cold

Acclimatization to heat is mainly accomplished in a week to fourteen days It consists primarily of a blood dilution and an increase in circulating blood volume This relieves the heart of some strain and after acclimatization individuals can perform work at a rate which was impossible before without great cardiac acceleration, a rise in body temperature and excessive fatigue Other compensatory adjustments which protect against overheating also occur, such as increased sweating, but these have little reference to the theme of this monograph and they have been well described in articles on acclimatization by Dill (1938), DuBois (1948), Newburgh (1949), Selle (1952), Hertzman (1955), and many others

Acclimatization to cold has also been much studied (Spealman, 1949, Kark, 1951 Selle 1952 Carlson *et al*, 1953 Carlson, 1954 Irving and Krog 1955) Better evidence of this increased ability to withstand cold is available from studies of animals than from studies of man There is less tissue injury and longer exposure to severe cold can be endured by acclimatized laboratory animals than by animals not previously exposed to cold This adaptation requires 3 to 5 weeks to develop and it persists for a week or more after removal to a normally warm environment. In men accustomed to life in the arctic, blood flow in the extremities and general resistance to cold injury seems to be improved The capability of the body to produce heat is also greater (Meehan 1955) It must be admitted that the participation of the heart in immediate and long lasting adjustment to cold is entirely secondary A degree of cardiac stress is involved in compensation for cold as well as in compensation for excess heat. Cardiac failure is a factor in the terminal phases of the collapse of resistance to heat and cold but sufficient has been said concerning this for the present.

THE EFFECTS OF HEATING AND COOLING THE HEART

The temperature of the heart has been changed by diathermy (Wiggers and Orias 1932 Prec et al, 1949a) by immersion of animals in hot or cold water (Hegnauer et al 1950 1951b, Kao et al 1955 Krog 1955) by cooling the surrounding air (Hamilton *et al* 1937), by covering the body with special pads through which cooled fluids were circulated (Talbot, 1951 Lewis and Taufic 1953), by perfusing isolated hearts with cooled or heated fluids (Knowlton and Starling 1912, Juvenelle et al. 1954) or by giving warm or cold blood transfusions to intact animals (Gollan, 1952 1954) The results observed have been much the same with all methods employed although there have been some differences caused by exposure of the heart and by the means employed for measuring cardiac temperatures and recording cardiac responses The tolerance of the unexposed heart is much greater and it has also been found that the use of cardiac catheters is likely to provoke arrhythmias in the cooled heart which otherwise might not occur until much lower temperatures are attained (Hegnauer et al 1951a)

Two factors appear to be important in influencing the effects of temperature on the heart. These are the rapidity of temperature change and

the production of temperature gradients within the heart created by the processes of heating and cooling that organ

LOCALIZED HEATING AND COOLING OF THE HEART The occurrence of arrhythmias and actual fibrillation of the auricle and even the ventricle is an all too common consequence of cooling and/or rewarming a subject or of cooling and warming the heart itself It has already been pointed out (Chapter VI) that localized heating or cooling may produce arrhythmias or actual fibrillation Heating of any portion of the myocardium so accelerates processes occurring there that ectopic beats may originate in the heated area (Eyster and Meek, 1921, Hellerstein and Liebow, 1950, Scott and Reed, 1951) Localized heating might also cause such a shortening of refractory phase and such an accelerated conduction that a disorganization of the entire myocardium would result but this rarely occurs possibly because it is difficult to set up much of a gradient in the normal warm heart Cooling is more likely to establish a potential gradient capable of creating an ectopic focus of beat origin and this has proved to be the case (Scherf et al, 1953) Pouring warm saline on an exposed fibrillating heart may actually result in a defibrillation but cold fluids thus applied actually tend to prevent defibrillation by electric shocks (DiPalma, 1952) Localized warming of the chilled heart evidently can be performed in some species with impunity (Crismon and Elliott, 1947), but in most cases fibrillation would be a likely consequence of such a procedure

It has been generally accepted that even under normal conditions all portions of the heart are not at a uniform temperature The intrinsic gradients may be exaggerated by the inrush of cold blood from the periphery during immersion produced hypothermia or when in attempting restorative measures supercooled blood trapped in the periphery by vasomotor occlusion is suddenly released to return to cool the heart still more (Ferrer, 1951, 1953) Also the sudden return of warmed blood to the cooled heart frequently appears to result in periodic arrhythmias or even fibrillation (Hegnauer 1952) It is certainly true that when thermocouples are placed within the right auricular chamber on the surfaces of auricle and ventricle and within the left ventricular wall (Pinkston et al, 1955) very marked gradients develop during cooling and rewarming but such studies have not been carried far enough to justify statements other than that marked gradients are present when the heart is susceptible to fibrillation or is difficult to defibrillate

Hoff and Stansfield (1949) found that localized cooling established an "injury current" between the normal and the cooled area. It is well recognized that such currents established by sharp temperature gradients may initiate propagated activity in tissues Local cooling does initiate arrhythmias and fibrillation and generation of such current flow may be the cause but there are other factors to consider Conduction within cooled areas is slow and this provides opportunity for reentry Stimuli applied in or near a cooled area will frequently initiate fibrillation if the local cooling does not immediately do so Regardless of whether reentry or the establishment of ectopic foci of beat origin is responsible for fibrillation, it certainly is true that localized cooling of a warm heart or local warming of a cooled heart is to be avoided in employment of hypothermia unless fibrillation is desired

THE EFFECTS OF GENERALIZED COOLING OF THE HEART Following an initial increase in rate there is a progressive fall as the heart is cooled In most studies a direct relationship was found between rate and heart temperatures within certain critical ranges but outside these limits this linearity was lost and the expression of the total relationship was curvilinear (Knowlton and Starling 1912 Badeer, 1951 Hegnauer, 1952 Kao et al. 1955) The heart stops beating regularly at a temperature of about 13 C but continues to beat sporadically down to 8° C. When rewarmed to 10° the heart beat starts again and at about 30° C. the heart can again replace the pump-oxygenator which must be employed in experiments involving cooling below 13 C. (Gollan 1954) At 15° 17 C. pulse rates fall to about 20 per minute and asystole or fibrillation frequently eventuate but failure may even occur at 20° 25° C. in some instances Spontaneous arrhythmias are a common consequence of such cooling (Talbott, 1941 Alexander 1946 Hegnauer 1952 1955) but they are more likely to occur as a result of abnormal stimulation by catheters or other manipulations (Hegnauer 1951a)

Reflex influences are minimal or absent at heart temperatures below 25 C. (Hegnauer et al. 1950) but the vagus is still capable of exerting some effect and epinephrine will still cause acceleration though fibrillation is most likely to occur (Scott and Reed 1951 Berne 1954b)

There appears to be no doubt that in the initial stages of cooling cardiac output rises probably due to shivering and autonomic compensatory activity (Prec et al., 1949b Hegnauer and D Amato 1954), but at low temperatures the output drops For example at 20° C. heart tem

the production of temperature gradients within the heart created by the processes of heating and cooling that organ

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perature the output is only 10-14 per cent of normal in the dog (Bigelow et al. 1950b Hegnauer and D Amato 1954) Recent work by Kao et al (1955) shows that cardiac output in the 25 to 30 lb dog does not fall much between heart temperatures of 38° 28° C. It remains at approximately 1.5 to 1.23 liters per minute but below this temperature range it begins to fall. At 27° C. it is 0.8 liters per minute and at 23.5° C. only 0 65 liters per minute. Stroke volume tends to rise as rate drops on cooling At 39 0° it is 16 6 ml. per beat and at 27 8° C. 39.8 ml. per beat. When oxygen consumption is related to cardiac output it is found that at low temperatures the ratio of cardiac output to oxygen consumption is higher This indicates that at low temperatures the heart really pumps more blood in relation to oxygen consumption of the body which is the reverse of what occurs in exercise (Kao and Ray, 1954) and this favorable situation persists until the occurrence of arrhythmias, asystole or respiratory failure.

Cooling the heart itself leads to a diminished coronary flow (Anrep and Hausler 1929 Berne, 1954b) but the reduction in metabolism is comparable and there is no evidence of oxygen lack. The heart can extract adequate O_2 from blood despite the movement of the dissociation curve to the left and despite a lessened coronary flow (Penrod 1951 Berne 1954a) It is even stated by Bigelow et al. (1950a) that at a temperature of 20° C. the heart can be excluded from the circulation for 15 minutes without suffering permanent injury and Gollan (1954) was able to revive a dog heart held at 4-0° C. without blood supply for one hour The oxygen requirement at such low temperatures is minimal and coronary blood flow generally exceeds requirements. Arteriovenous oxygen difference is normal and there is no evidence of an oxygen debt after rewarming (Hegnauer, 1952 1954) Estimation of myocardial function by pulse contour analysis reveals no myocardial impairment at low temperatures (Berne 1954a) There is a marked prolongation of systole and of the isometric relaxation phase but myocardial competence is not interfered with if the heart is permitted to maintain a slow rhythm. If the cooled heart is driven at a rate much above that which it naturally assumes coronary flow decreases cardiac filling is insufficient because of short diastole and cardiac output and arterial pressure fall (Berne 1954b)

On cooling there is an increase in the hematocrit, a raised blood viscosity and a probable decrease in blood volume but at levels of cooling usually attained these changes do not embarrass heart action There is

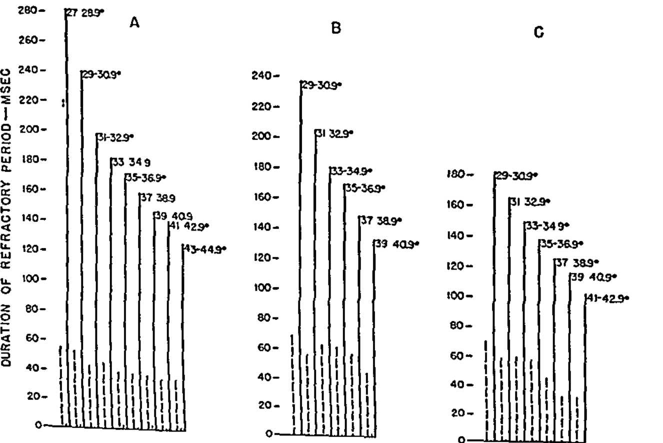


FIGURE 38. Effect of temperature on the total (——) absolute ( ) and relative (– – – – –) refractory periods of the ventricle driven by way of the auricle (A) of the directly driven ventricle (B) and of the directly driven auricle (C) Averages of 28 acute experiments.

a metabolic acidosis at low temperatures (Hegnauer and Covino 1955 Kao et al 1955) and this may affect the responses of the heart but the role of pH change in the determination of cardiac excitability and vulnerability to fibrillation has not been ascertained.

Diastolic thresholds for the production of extrasystoles of the dog heart are not consistently affected (Pinkston et al., 1955) As an example in one experiment ventricular thresholds were 0 13 ma. at 39 4° C. and 0 17 ma at 26.2° C while in the auricle they were 0 19 ma at 39 7° C. and 0 18 ma at 26 7° C. All changes observed in the 30 animals studied were usually in hundredths of a milliampere

The refractory period on the other hand is markedly affected by cooling the heart. The lengthening of the total refractory period of the ventricle is due almost entirely to a prolongation of the phase of absolute refractoriness. This lengthening shows a linear relationship with change in temperature. The relative refractory period, however is not consistently changed (Fig 38) At extremely low temperatures the rate of prolongation of refractoriness falls off and the relative refractory period is slightly lengthened (Brooks et al 1952, Pinkston et al., 1953 1955) This is evidence that the processes involved in the terminal phases of recovery from excitation are less susceptible to modification than are the earlier occurring physico-chemical changes These same conclusions hold for the auricle but the effects observed are variable

Figure 39 shows that strength interval curves shift in position as the heart is cooled. There is no consistent change in amplitude or duration of the dips. The heart is most vulnerable during the intervals of the dips (Hegnauer and Covino 1955) but the effects of cooling on fibrillation thresholds and duration of vulnerable periods have not been determined One fact is clear however the *cooled heart is* more susceptible to fibrillation and auricular fibrillation or less frequently ventricular fibrillation develop spontaneously in both anesthetized and unanesthetized hypothermic man and other animals

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FIGURE 39 The effect of temperature on the excitability and refractory periods of dog auricle and ventricle as indicated by strength interval curves. Studied by means of chronically implanted electrodes (A and B) *and in* acute preparations (C and D)

A.	Auricle	38.2 C (•—•)	31.0 C (o— — —o)	26.0 C (x— — —x)
B.	Ventricle	38.0 C (•—•)	31.0 C (o— — —o)	25.8 C (x— — —x)
C.	Auricl	36.8 C (•—•)	35.0 C (o— — —o)	31.9 C (x— — —x)
D	Ventricle	40.0 C (•—•)	37.6 C (o— — —o)	28.7 C (x— — —x)

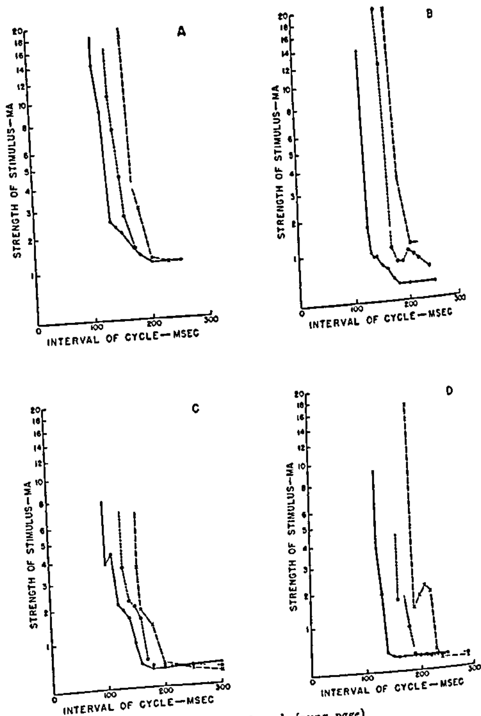


FIGURE 39 (*See legend facing page*)

44° C. (Wiggers and Orias, 1932) Knowlton and Starling (1912) found that irregularities of rhythm began in the heart lung preparation at 40° C. but the heart continued to beat even at 46° C. In recent work on isolated tissues such high temperatures were not found compatible with prolonged activity

Warming the heart increases coronary flow (Anrep and Häusler, 1929) Oxygen consumption of the heart rises by well over 60 per cent between 38° and 42° C. In experiments by Prec at al. (1949a) the arteriovenous oxygen difference was 6 1 vol. per cent at 38° C. and 11.3 vol. per cent at 42° C. Cardiac output remains about the same between 33° and 40° C but at both extremes output begins to fall This failure is due to decreased venous return resulting from peripheral dilatation of the vascular bed and an inability of circulatory volume to increase to a commensurate d gree Similar observations concerning cardiac output changes have been made by Scott, Bazett and Mackie (1940)

When attempts were made to determine the effects of high heart temperatures on cardiac excitability conduction, refractory periods, and latency of response (Brooks et al., 1952 Pinkston et al. 1953 1955) only minor effects were manifest until heart temperatures above 39° C. were attained. Diastolic threshold was not changed markedly but refractory periods were shortened as were conduction times and latencies. The QT interval was reduced and duration of the QRS complex was shorter

The all too frequently encountered contradictions in the literature with respect to the degree of change in electrical or mechanical responses of the heart, when it is heated or cooled to various extents are difficult to explain It should be pointed out however that temperature change affects many different parameters of function and modifies to different degrees the numerous processes involved in production of all the phenomena and reactions recorded Conditions imposed upon the heart vary enormously The rate of heating and cooling and the means employed in establishing the desired degree of temperature change are all so varied that uniformity of result could not be expected. The most refined studies of temperature effects have been carried out on individual cardiac fibers by means of intracellular recording techniques and these results will be considered next.

THE REACTIONS OF CARDIAC CELLS AT VARIOUS TEMPERATURES

The method of introducing a microcapillary electrode into a single element of a multifiber preparation has made it possible to measure the

Conduction times and latencies of response are lengthened by cooling the heart The QRS complex is prolonged as is the QT interval A V dissociation occurs in hibernating animals and in nonhibernating species 2 1 or 3 1 block often occurs at low temperatures There is evidence that junctional tissue is most susceptible to cooling One of the most striking features is that refractoriness appears to be prolonged out of proportion to the lengthening of the QT interval (Schutz, 1936) This tends to support the conclusion, to be discussed later, that repolarization of the membrane in the cooled heart appears to be completed before recovery of normal excitability

The slowed conduction and the minor change in excitability, the disproportionate changes in various cardiac tissues, and the possibility of augmented temperature gradients in the heart give some clue as to why during cooling and rewarming both auricular and ventricular fibrillation are prone to develop Other observations have also been made which indicate that in the cold a fractionation of activity within the myocardium occurs, which gives the appearance of a loss of latency (DiPalma, 1955)

Numerous suggestions have been offered as to the cause of death in hypothermia Respiratory failure may be a primary or contributory cause If artificial respiration is given the heart can continue an adequate function *It appears that asystole and fibrillation are the usual causes of death* in such circumstances While defibrillation of the cold heart is not difficult (Pinkston et al, 1955), driving the asystolic heart even at slow rhythms is often practically impossible These effects of cooling even to 10° C or 4° C are reversable on rewarming if long continued fibrillation can be prevented

THE EFFECTS OF INCREASED CARDIAC TEMPERATURE In contrast with studies of the effects of cold very few attempts have been made to assay the results of cardiac hyperthermia The usual discussion has been carried on as to whether or not there is a linear or curvilinear relationship between the rise in heart rate and body or heart temperature (Clark, 1927, Tanner, 1951) This rise in rate is relatively slow between 37 4° C (155 beats/min) and 42° C (200 beats/min) in the dog but then accelerates and at 43 5° C the heart rate is 345 beats/min It is approximately at this temperature that collapse begins and death occurs as heart temperatures of approximately 44 5° C are attained Arterial blood pressure remains relatively constant from 37° C to 41.2° (145/105), rises to 250/100 at 43 6° C and then falls precipitously at

44° C (Wiggers and Orias 1932) Knowlton and Starling (1912) found that irregularities of rhythm began in the heart lung preparation at 40° C. but the heart continued to beat even at 46° C. In recent work on isolated tissues such high temperatures were not found compatible with prolonged activity

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THE REACTIONS OF CARDIAC CELLS AT VARIOUS TEMPERATURES

The method of introducing a microcapillary electrode into a single element of a multifiber preparation has made it possible to measure the

absolute value of the cardiac membrane potential and to obtain a faithful record of the potential changes during activity Quantitative measurements of temperature effects on the individual fibers of the hearts of various species have been made by a number of workers Temperature produced changes in frog ventricle (Woodbury, Hecht and Christopherson, 1951), in cat auricle (Burgen and Terroux, 1953), in dog Purkinje fibers (Trautwein et al, 1953), in "false tendons" of calf and sheep hearts (Coraboeuf and Weidmann, 1954) and in papillary muscle of cats and dogs (Hoffman and Suckling, 1956) have been studied

The temperatures to which these isolated tissues were exposed ranged from 50° to 4° C and in some instances the actual tissue temperatures were measured by means of resistance thermometers (Standard telephones type F2311/300) placed only a few mm from the tip of the recording microelectrode (Coraboeuf and Weidmann, 1954) or by other adequate recording devices in contact with the tissue strips The results of Coraboeuf and Weidmann (1954) provide a good basis for describing the effects generally observed when the temperature of heart cells is raised above or lowered below normal ranges of variability

At 38° C the "false tendons" of the sheep and calf hearts beat at approximately 48 beats/min Lowering of the temperature results in a slowing of this rhythm and a cessation of spontaneous activity at temperatures of 25° 15° C When recording electrodes are in pacemaker tissue and record the typical prepotential (the upward concavity in the voltage time curve starting some 50 to 100 msec before upstroke of the propagated action potential) it can be seen that a fall in temperature slows the potential time course in all its phases but does not have any appreciable effect on the threshold potential for spontaneous firing (60 mv over a temperature range of 40° 25° C) nor on the shape of the action potential until the greatest extremes of temperature are reached Hyperthermia shortens the potential time course initially but the highest temperatures impair the responses (Coraboeuf and Weidmann, 1954) In the Purkinje pacemaker, within the temperature range specified, the rate of the slow diastolic depolarization has a Q_{10} of 5 (a change of 500 per cent for 10° change in temperature) and is consequently much more susceptible to temperature change than are other changes involved in the production of the action potential (Trautwein, 1953)

The value of the resting transmembrane potential (94 mv at 38° C) and the reversal potential or "overshoot" (35 mv at 38° C) do not change

appreciably at temperatures within the range of 40° and 25° C. Outside these limits both the resting potential and the 'over hoot decrease (Coraboeuf and Weidmann 1954) Trautwein (1953) found that the Q_{10} of both the transmembrane resting and action potential of Purkinje fibers of the dog heart is 1 0 between 25° and 40° C A lowering of the temperature from 25° to 16° C. produces a much greater change and the amplitude of the action potential falls from 120 mv to 40 mv while membrane potential as determined by means of intracellular recording falls from 90 mv to 55 mv In the frog ventricle over a range of 0.2 to 30° no effect on resting membrane potential could be observed (Woodbury et al 1951) In this work variability between fibers was such that the authors felt changes might be ma ked but it is to be expected that amphibian tissue might have characteristic properties of its own (Coraboeuf and Weidmann 1954)

The depolarization of heart cells which occurs at low temperatures is reversable Purkinje fibers can be kept at 4° C for 24 hours or longer and then on rewarming will polarize again and not only establi h normal tran membrane potentials but will also begin rhythmic activity Cold can block fiber activity in both a depolarized and polarized state At critical levels of cooling the plateau will continue almost indefinitely on rewarming the terminal steps of repolarization occur This indicates that cold can block both depolarization and repolarization processes and reports of tudies on the intact heart tend to confirm this conclusion

The durations of the various phases of the transmembrane action potential are affected to different degrees The Q_{10} value for the upstroke of the potential is 1 7 for the descending limb of the initial spike (the reversal potential) 1 9 for the plateau 4 5 and for the final phase of repolarization 2 6 The difference between the temperature coefficients of the plateau and the final phase of repolarization is in agreement with its different sen itivity of the absolute and relative refractory period to cooling The Q_{10} for the slow diastolic depolarization of pacemaker tissue was 6 2 in Coraboeuf and Weidmann s (1954) studies The drop in contraction frequency contributes to the prolongation of the action potential and the recovery process Under such circumstances a drop in temperature from 40 to 25° C. increases duration of the action potential more or less exponentially from 500 m ec to 1600 msec Even when the fibers are driven at a constant rate of 55 beats/min similar degrees of cooling prolong action potential duration to 950 msec. (Trautwein 1953)

The "passive" electrical properties of Purkinje fibers are also affected by cold The axoplasm resistance and the membrane DC resistance increase on cooling and have a Q_{10} of 1 5 (Coraboeuf and Weidmann, 1954)

Simultaneous surface and transmembrane action potential records demonstrate that the onset of depolarization coincides with the beginning of the QRS complex and the last phase of repolarization with the T wave. The duration of the surface recorded and transmembrane potentials is a function of heart rate and/or heart temperature It was pointed out by Schütz (1936) that repolarization in the cooled heart is completed before recovery of normal excitability of the membrane It is possible however that the terminal phases of repolarization are much longer and are not detected by amplifications standardly used in such recording

Another seeming contradiction between results obtained from the work on individual fibers and that on the total heart is the fact that the terminal phases of repolarization have a very high Q_{10} but the relative refractory period seemingly is not much affected by heart temperature changes The period of relative refractoriness corresponds only to the terminal phases of this fast repolarization and thus the comparison is not justifiable

SUMMARY

Heart action is such as to participate in the adjustment required for maintenance of a constancy of body state during exposure to extremes of heat and cold A rise in cardiac output in hyperthermia results from a necessity to increase heat loss by maintaining a greater *blood flow* in body surface tissues A rise in output during hypothermia is occasioned by shivering and the greater need of muscular tissues for *blood* The peripheral and central mechanisms essential to these adjustments are described Acclimatization and the change in heart function associated therewith are discussed

The consequences of cooling and heating the heart are described Localized cooling and heating create gradients of potential and activity which are favorable to the production of arrhythmias and fibrillation The changes in rate, cardiac output blood pressure, conduction rate, refractoriness and excitability are described Tolerance of the heart for temperature extremes and the causes of failure of function occasioned by heating and cooling are discussed Failure at low temperatures may result from asystole but about as commonly from fibrillation, particularly if the heart is stimulated by one means or another when in a hypothermic state

Studies of the effect of temperature change on individual cardiac fibers are summarized. Results of such work give a more direct indication of the changes produced in the heart by heating and cooling. Heating accelerates and cold retards spontaneous depolarization in pacemaker tissue; the same is true of repolarization following activity. At extremes of temperature the transmembrane potential is reduced and an actual depolarization occurs which is reversable providing it has been produced by cold.

The range of temperatures which effect changes endangering the function of the heart and its cells are known and many of the serious reactions occasioned by or made possible by cooling or heating of the heart have been described.

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VIII The Effects of Heart Rate, Action of Autonomic Nerves and Chemical Mediators on Cardiac Excitability

The changes in refractoriness vulnerability to fibrillation, duration of the transmembrane action potential speed of *conduction, and threshold to electrical stimuli are discussed* in relation to heart rate and action of autonomic mediators

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THE EXCITABILITY CYCLE of the dog heart under standard conditions has been described in the preceding chapters and the relationships between changes in excitability and membrane phenomena have been discussed in some detail However, the recovery of excitability is not fixed to a single time course in cardiac muscle, numerous factors operative in physiological adjustments to altered body function markedly change the excitability cycle At times alterations in refractoriness are accompanied by changes in resting excitability, rhythmicity, or conduction velocity, at other times refractoriness is the *only variable Because of the complex* and often unpredictable relationships between these several aspects of cardiac excitability, the effect of a number of factors known to influence the cyclic loss *and recovery of excitability and irritability of heart* muscle associated with each heart beat have been studied In the present chapter the influence of heart rate and autonomic activity will be considered in detail

HEART RATE CHANGE—THE EFFECT OF CYCLE LENGTH ON EXCITABILITY

Early myographic studies revealed a definite relationship between the frequency of contraction of the heart and the duration of systole Subsequently, electrocardiographic recording techniques were employed in an attempt to relate the duration of electrical activity to the frequency of the beat both in experimental animals (Ashman et al, 1945) and in man (Levine et al, 1951) All studies were in agreement insofar as all demonstrated that at faster rates the heart recovered excitability more quickly However, the underlying mechanism of this hastened recovery remained uncertain as did the exact relationship between rate and the duration of

refractoriness (Bazett, 1920 A hman 1942 Schlamowitz 1946) Further more in many of these experiments factors other than frequency of con traction such as varying vagal and sympathetic tone were operative in influencing excitability For the same reasons results obtained in different studies were often in disagreement. Because of this reinvestigation of the problem seemed worth while

In the experiments discussed below the effect of a single variable—cycle length—on resting excitability refractoriness and conductivity of the auricle and ventricle has been determined in the intact heart. Except in the section devoted to transient changes in excitability resulting from extrasystoles all results are those obtained after complete equilibration at each heart rate The most important point concerning methodology is that the changes in cycle length resulted from driving stimuli applied at any desired frequency alterations in vagal and sympathetic activity and changes in blood pressure were avoided as were extremes of rate which might have resulted in any form of cardiovascular insufficiency In these same experiments the duration of refractoriness was related to both the local cardiac electrogram and the limb lead electrocardiogram In addi tion the effect of the same range of rates on transmembrane potentials of single fibers was studied in the isolated papillary muscle In this manner the behavior of the individual unit as well as that of the entire population of myocardial fibers was evaluated. The latter technique also gave an excellent indication of whether or not any factors other than cycle length influenced results obtained from intact hearts.

THE RECOVERY OF EXCITABILITY The effect of an increase in rate on the recovery of excitability of the dog s ventricle as seen in Figure 40, is indicated by a di placement of the strength interval curve to the left without alteration in its configuration Thus the hastened recovery at higher rates is accomplished by means of a parallel shortening of both the absolute and total refractory periods The relative refractory period is unchanged by variations in rate as shown in Figure 40-C, D neither the duration nor course of recovery of this subdivision of the refractory period is altered by a step-wise increase of heart rate from 100 to 300 beats per minute (Siebens et al 1951) These observations concerning the recovery of excitability are the same whether the ventricle is driven di rectly or by means of stimuli applied to the auricle

The results obtained suggest that at higher rates the heart begins to recover excitability earlier and earlier in the cycle but at all rates once

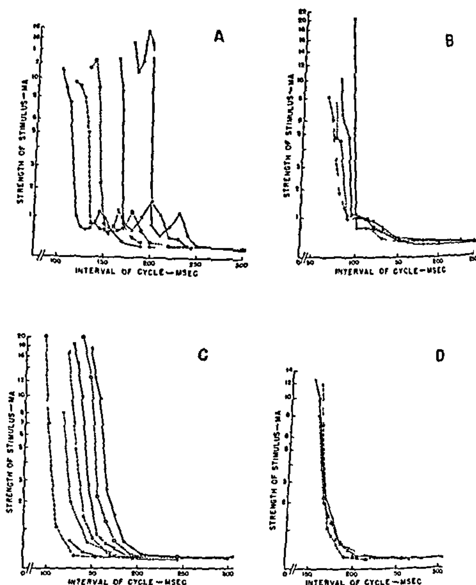


Figure 40 The effect of heart rate on recovery of excitability in the ventricle (A) and auricle (B) The heart rates (beats per min) in A from right to left are 92, 133 200 240 and 300 In B rates are 100 150 200 and 240 C shows another *family* of ventricular curves which are superimposed in D to show the constancy of the time course of recovery, rates are 100 120 150 171 200 and 300

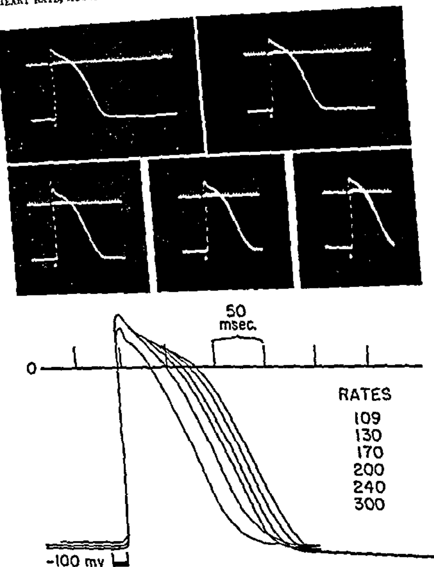


FIGURE 41. The effect of heart rate on the transmembrane potentials of a single ventricular fiber. The actual records obtained (at top) are superimposed in the tracing (at bottom) to emphasize the fact that once repolarization begins it proceeds at a constant velocity at all rates. (Reproduced from Hoffman and Suckling, 1954.) (Retouched to show action potential upstrokes by dotted lines.)

recovery starts it proceeds to completion at the same velocity That this is indeed the case is shown by the configuration of the action potential recorded from single ventricular fibers (Fig 41) Such records of the time course of depolarization and repolarization of the cardiac muscle membrane demonstrate that at high rates only the duration of the plateau of the action potential is progressively shortened, the time course of re polarization, however, is unchanged (Hoffman and Suckling, 1954) This similarity between results obtained in intact animals and isolated muscle preparations strongly suggests that in the former case the only significant variable is the cycle length

The effect of changes in heart rate on the recovery of excitability of auricular muscle is essentially the same as in the case of the ventricle (Fig 40 B) However, because of the greater difficulty experienced in ac curately delineating the duration of the absolute and total refractory periods of auricular muscle, it is impossible to state with certainty whether or not in this tissue there is some change in the duration of the relative refractory period when heart rate is varied

THE IRRESPONSIVE PERIOD The boundary of the irresponsive *period of ventricular muscle bears a constant relationship to the* end of the total refractory period at all heart rates studied (Siebens et al, 1951) This correlation is a natural consequence of the common origin of the irresponsiveness and refractoriness (see Chapter IV) The propagation of a response depends upon propagated excitation and this in turn is related to the excitability of the cell and the potency of the intrinsic excitatory process both are subnormal during the refractory period

THE RELATIONSHIP BETWEEN REFRACTORINESS AND ELEC TRICAL ACTIVITY As demonstrated in Chapters IV and V both the end of the refractory period of cardiac muscle and the repolarization of the muscle membrane bear a constant relationship under normal conditions to the T deflection of the electrocardiogram or the local cardiac electro gram Specifically when the unipolar electrogram is recorded from a site immediately adjacent to the test electrodes, the end of the total refractory period coincides approximately with the positive peak of the T wave This is in complete agreement both with MacLeod s (1938) analysis of the cardiac electrogram and with the results obtained by recording the local bipolar electrogram from the same area with contiguous punctate electrodes Such tracings clearly demonstrate that repolarization of the muscle in the immediate vicinity of the test electrode occurs simul

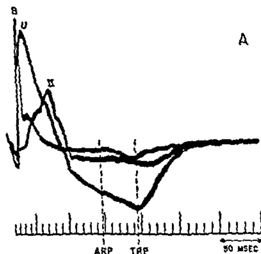
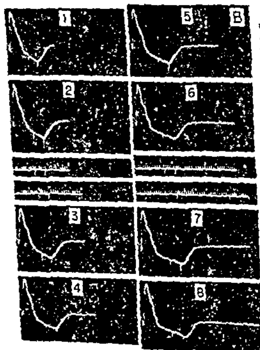


FIGURE 42. A Relationship of absolute (ARP) and total refractory period (TRP) to simultaneously recorded bipolar (B) unipolar (U) electrograms and to limb lead II electrocardiogram.



B The effect of rate on the unipolar electrogram and the termination of ARP (left hand pip) and TRP (right hand pip) Cycle lengths 1—250 msec., 2—300 msec., 3—350 msec., 4—400 msec., 5—450 msec., 6—500 msec., 7—550 msec., 8—600 msec. Time scale is 50 and 10 msec. Notice constant duration of relative refractory period and relationship of T wave to termination of TRP

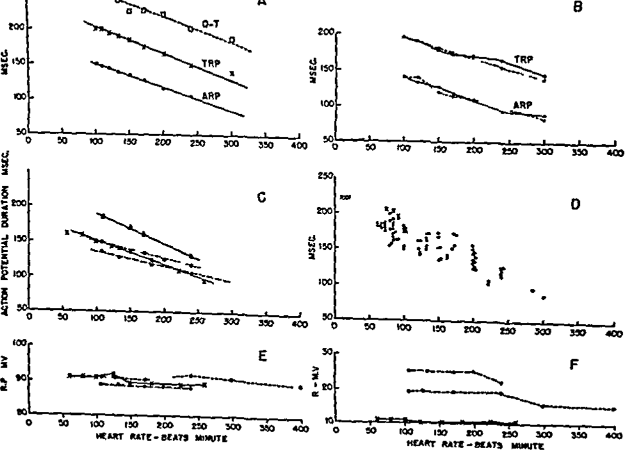


Figure 43 Effect of heart rate on ventricular (A) and auricular (B) refractoriness (ARP absolute TRP total refractory periods Q T interval of the limb lead ECG) The effect of heart rate on the duration of ventricular transmembrane action potentials of four separate single fibers at various rates (C) and many different fibers at each rate (D) The resting potential (E) and reversal (F) of individual ventricular fibers at different heart rates

taneously with the end of the total refractory period (Siebens et al, 1951) Such deviations as are noted result from the difficulty with which the time of recovery of full excitability is ascertained This is due to the very gradual slope of that portion of the strength interval curve which indicates the transition from partial refractoriness to full recovery of excitability

The temporal relationship between the local unipolar and bipolar electrogram the limb lead electrocardiogram and the duration of refractoriness is shown in Figure 42 A. As would be expected from the results discussed above, this same relationship is constant over a wide range of rates (Fig 42 B) Furthermore since the time course of repolarization does not change the configuration and polarity of the electrogram T deflection are unaltered. When T wave changes are associated with tachycardia (Garb and Chenowith, 1953) factors other than cycle length must be operative in their production

A number of formulations have been published to express the mathematical relation hip between the duration of electrical activity in cardiac muscle (Q T interval) and the frequency of contraction (Bazett, 1920 Schlamowitz 1946 Woodbury et al. 1951) In the case of the dog's ventricle, beating at rates from 60 to 250 beats/minute this relationship is linear (Siebens et al 1951) In Figure 43 the parallel shortening of Q T interval, the total refractory period and the absolute refractory period that results from an increase in heart rate is demonstrated A similar relationship obtains between the duration of the transmembrane action potential of a single ventricular fiber and the frequency of contraction (Fig 43)

LIMITS OF LINEARITY At higher rates shortening of the cardiac cycle is achieved not only by means of a decrease in the duration of the recovery phase but also by a decr ase both absolute and relative, in the duration of the period of full excitability Thus the total refractory period at a rate of 90 beats per minute occupies 35% of the cycle allowing 65% of the time for the ventricle to rest in a recovered state. At a rate of 300 beats/min. the refractory period occupies 85% and diastole 15% of the cycle These results suggest the presence of a predictable maximum heart rate and also a limit to the linear relationship between rate, refractoriness and the Q T interval. Inspection of the data in Figure 43 indicates that this is indeed the case In any one dog the linear relationship between refractoriness the Q T interval, and heart rate is lost

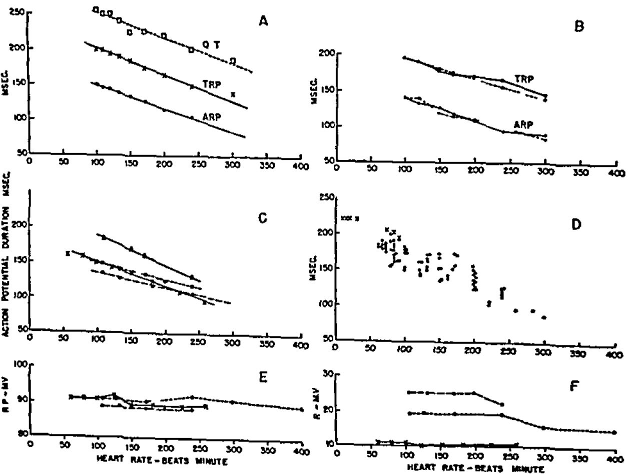


FIGURE 43 Effect of heart rate on ventricular (A) and auricular (B) refractoriness (ARP absolute TRP total refractory periods Q T interval of the limb lead ECG) The effect of heart rate on the duration of ventricular transmembrane action potentials of four separate single fibers at various rates (C) and many different fibers at each rate (D) The resting potential (E) and reversal (F) of 1 individual ventricular fiber at different heart rates.

quency of beat and the duration of refractoriness Q T interval, etc that have been described fail to apply Furthermore if the heart is driven at still faster rate each depolarization begins before recovery from preceding activity has been completed When this happens it is impossible to measure the end of repolarization and the time of complete recovery of excitability There are also additional changes which complicate the results obtained Since the excessive rate prevents complete repolarization, the resting and action potentials decrease in magnitude (Fig 43 E, F), also because of the incomplete repolarization the threshold is altered and the conduction velocity of each propagated beat is slowed (see Chapters II and IV) Such changes in threshold and conductivity will be discussed below

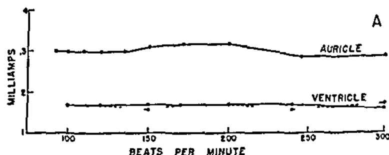
DIASTOLIC EXCITABILITY Variations in the frequency of contraction of cardiac muscle within a range of approximately 60-250 beats/minute have no effect on the level of resting excitability of either auricle or ventricle demonstrating that both tissues are capable of complete recovery of excitability within the time limit imposed by the cycle length (Fig 44-A) The observation that the resting membrane potential of a single fiber of the papillary muscle is likewise constant throughout a similar range of rates (Fig 41 and 43) and even during periods of prolonged diastole (Hoffman and Suckling 1954) is in agreement with this interpretation Furthermore in preparations demonstrating a period of supernormal excitability changes in rate fail to produce any consistent modification in either the magnitude or duration of this phase of the cycle

CONDUCTION VELOCITY The conduction velocity of the driven beats in either auricle or ventricle is not affected by rates up to 250-300/minute (Fig 44-B C) This would be expected in view of the absence of change in the level of resting excitability in either chamber and the fact that in both the recovery of excitability is completed before the next depolarization occurs

In marked contrast to this is the effect of an increase in heart rate on A V conduction velocity (Fig 45 A) Here the conduction time becomes progressively longer at higher frequencies emphasizing an essential difference between specialized and nonspecialized myocardial tissues Perhaps the explanation for this observation will be found when the nature of the normal A V delay has been determined Certainly at higher rates the longer refractory period of Purkinje fibers may contribute to this finding It should be mentioned that the slowing of A V conduction

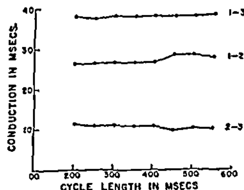
at a frequency somewhere between 250 350 beats per minute and the rate of shortening of these variables diminishes A similar lack of linearity is found at excessively slow rates (Fig 43)

The underlying cause of this failure to maintain a linearity of change in ventricular muscle as heart rate is accelerated above a certain level is apparent from the records shown in Figure 41 When the transmembrane potentials of a single ventricular fiber are recorded at similar rapid rates, a new phenomenon is observed This consists of a regular alternation in the shape and duration of every other action potential so that on alternate beats there is loss of the plateau and a different time course of repolarization Because of this the relationships between fre-









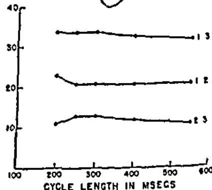


FIGURE 44 The effect of heart rate on A—auricular and ventricular diastolic thresholds B—ventricular and C—auricular conduction velocity Insert shows position of electrodes on heart driving cathode (D) testing cathode (T) and three pairs of recording electrodes (1 2 3) Interelectrode conduction time between various pairs shown in graphs

which results when the heart is artificially driven at faster rates is not observed when the tachycardia is produced by a decrement in vagal and an increment in sympathetic activity In this latter case a shortening of the PR interval occurs as a result of the specific action of the autonomic mediators on the junctional tissue and perhaps on the specialized conducting fibers

TRANSIENT CHANGES IN CYCLE LENGTHS Studies of the effect of transient changes in cycle length serve to emphasize the importance of studying heart rate only under conditions of complete equilibrium. As seen in Figure 46-C, D repolarization following each beat changes progressively for many cycles of activity before a steady state is attained. Similarly when the rate is abruptly altered in a rhythmically beating papillary muscle the recovery limb of the transmembrane action potential shortens slightly on each successive cycle and reaches a condition of equilibrium only after a considerable lapse of time (Fig 46-A, B) Such a slow progressive adjustment occurs both when the cycle length is increased and when it is decreased. Studies of changes in excitability performed during such periods of instability would obviously give

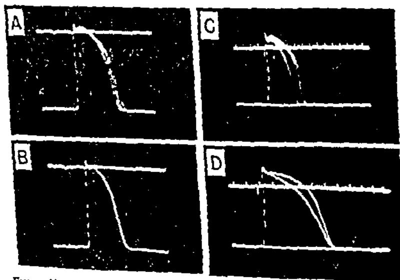


FIGURE 46 The effect of transient changes in cycle length on the transmembrane action potential. (Retouched to show action potential upstrokes by dotted lines.) A. Sudden increase in rate, reaching equilibration in B C, D First beats following prolonged period at quiescence.

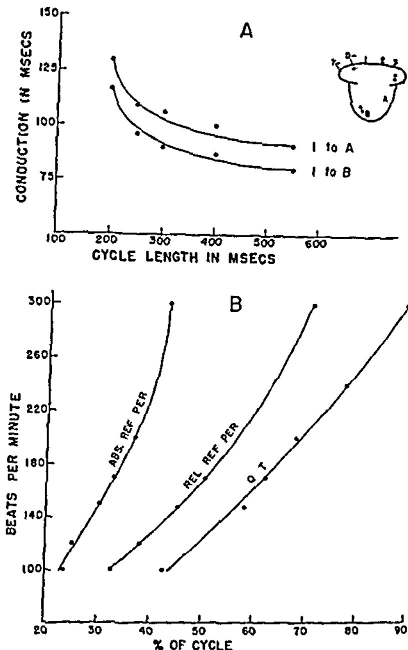


FIGURE 45 A Effect of changes in driven heart rate on auriculo ventricular conduction time Driving electrodes on rt auricle ventricular recording electrodes (A B), auricular recording electrodes (1 2 3)

B Proportion of cycle occupied by ARP RRP and QT interval at various heart rates

which results when the heart is artificially driven at faster rates is not observed when the tachycardia is produced by a decrement in vagal and an increment in sympathetic activity In this latter case a shortening of the P R interval occurs as a result of the specific action of the autonomic mediators on the junctional tissue and perhaps on the specialized conducting fibers.

TRANSIENT CHANGES IN CYCLE LENGTHS Studies of the effect of transient changes in cycle length serve to emphasize the importance of studying heart rate only under conditions of complete equilibrium. As seen in Figure 46-C, D repolarization following each beat changes progressively for many cycles of activity before a steady state is attained Similarly when the rate is abruptly altered in a rhythmically beating papillary muscle the recovery limb of the transmembrane action potential shortens slightly on each successive cycle and reaches a condition of equilibrium only after a considerable lapse of time (Fig 46-A, B) Such a slow, progressive adjustment occurs both when the cycle length is increased and when it is decreased Studies of changes in excitability performed during such periods of instability would obviously give

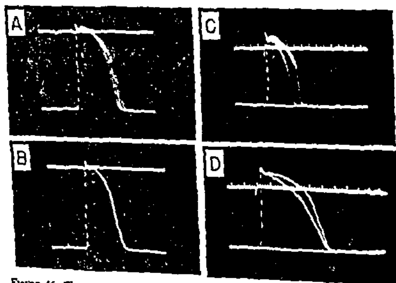


FIGURE 46. The effect of transient changes in cycle length on the transmembrane action potential. (Retouched to show action potential upstrokes by dotted lines) A. Sudden increase in rate reaching equilibration in B C, D First beats following prolonged period at quiescence.

quite inconsistent results and the relationships presented in preceding sections of the chapter would not be seen

The effect of single extrasystoles on the time course of recovery of membrane potential and excitability has also been studied in intact hearts and isolated papillary muscles Figure 32 in Chapter V shows the change in the action potential of both the extrasystole and the post extra systolic beat It is seen that while both are altered, the change in duration and configuration depends on whether the extrasystole is introduced early or late in diastole The refractory periods of such extrasystoles are usually shorter than those of driven beats, but the strength interval curve ob tained for them demonstrates the usual phenomena noted for normal rhythmic activity Additional studies of this nature have recently been carried out by other investigators (Moe et al, 1955)

SUMMARY It can be said that the most important effects of heart rate on excitability are as follows

1 When the strength interval curve is employed as a measure of cardiac excitability, the effect of an increase in heart rate is essentially to shift the curve further to the left This shift reflects progressive shorten ing of the absolute and total refractory periods without a change in the duration of the relative refractory period Neither the dip nor the mini mum diastolic threshold is altered by rates up to 250 300 beats/min The effects of rate on ventricular excitability are identical whether this chamber is being driven directly or through the auricle The effects of rate on the recovery of auricular excitability parallel those of the ventricle

2 Velocity of conduction of the propagated beat in either auricle or ventricle is not affected by rates up to 250 300 beats/min In other words, the capacity to conduct and the capacity to be excited are both capable of complete recovery within this range of rates

3 Conduction in the A V bundle slows progressively with the increase in rate This contrast with the effect of rate on conduction in auricular and ventricular myocardium indicates an essential difference between these specialized and nonspecialized conducting tissues

4 The Q T interval shortens progressively with rate This is a rela tive shortening, however, for although the Q T interval occupies but 40 to 50 per cent of the cardiac cycle at rates around 100, it occupies 80 to 90 per cent of the cycle at rates of 300 beats/min

5 The time of occurrence of the apex of the T wave bears a constant relationship at all rates studied to the end of the total refractory period

as well as to the earliest point in the cycle at which a stimulus delivered in the relative refractory period produces a propagated action potential This similarity of the effects of rate on the Q T interval and on the position of the boundaries of the total refractory period and irresponsive period tends to impress one with the significance of the T wave in terms of ventricular excitability

6 The transmembrane potential recorded from a single fiber of the isolated papillary muscle reveals the same effects of cycle length on the course of recovery as are found in the intact heart. These records also demonstrate that when excessively rapid rates are employed a new change —incomplete repolarization—supervenes Thus failure to attain a normal resting potential is the direct and immediate cause of the abnormal thresholds and conduction velocity which occur, as well as the cause of deviation from a linear relationship between heart rate and duration of the total refractory period or Q T interval. Such changes when encountered are thus only an indirect effect of cycle length. This finding explains many of the discrepancies noted between the results obtained by previous investigators

THE EFFECT OF AUTONOMIC ACTIVITY ON EXCITABILITY

1 *THE VAGUS NERVE AND THE AURICLE* In the preceding section of this chapter the effects of artificially induced variations in heart rate on the excitability of the auricle and ventricle have been discussed Normally such changes in rate result from fluctuations in the degree of tonic activity manifest by the sympathetic and parasympathetic cardiac nerves These nerves in addition to changing the frequency of contraction have a widespread effect on the excitability conductivity and contractility of cardiac muscle

The actions of vagal stimulation and of acetylcholine have been extensively studied in both mammalian and amphibian hearts (Andrus and Carter 1930 Ashman and Garrey, 1931 Gilson, 1935 1939 Schütz, 1936) and although their major effects on contractility and rhythmicity have been well known for many years (Wiggers 1919) the changes brought about in excitability and conductivity are not as well understood In many instances results obtained in the frog or turtle heart are assumed to indicate that a similar response is present in mammalian hearts although the reactions underlying the alterations in cardiac activity that result from vagal stimulation have received little experimental attention

The situation is much the same with respect to adrenergic nerves and *mediators* *Although the* major effects of epinephrine, nor epinephrine and sympathetic activation have been investigated by a variety of techniques and although the action of these agents on many parameters of cardiac function is known with certainty, disagreement exists concerning the *similarity or difference of the action of epinephrine and nor-epinephrine* on rate and rhythmicity (Ahlquist, 1948, Nathanson et al, 1950, Greenburg and Lambert, 1952), contractility and excitability (West, 1947, Lands and Howard, 1952, Greiner and Garb, 1950) of the heart. It is quite likely that nor-epinephrine is the *major mediator of cardiac sympathetic* nerve activity in mammals (Outschoorn and Vogt, 1952), on the other hand, the predominant neuro humor released on adrenal activation is epinephrine (Bulbring and Burn, 1949) It is of interest to know how these two agents differ, quantitatively and qualitatively, in their cardiovascular effects and to assess the role of each in homeostasis

These considerations have led to a study of the effect of vagal stimulation and acetylcholine on the excitability of the dog s auricle and ventricle, and to a detailed comparison of the actions of epinephrine, nor epinephrine and sympathetic nerve stimulation on these same tissues Some attempts have also been made to elucidate the mechanisms by which the observed changes in excitability are produced

The effects of vagal stimulation on auricular muscle The technique employed in testing the effect of vagal stimulation on the dog heart requires only a brief description Both nerves were divided high in the neck and the peripheral stumps were stimulated with sinusoidal pulses at a frequency of 20 per second The strength of the stimulus was graded on the basis *of the degree of A V block produced* "weak stimulation prolonged the P R interval by 20 50 msec "intermediate strength produced 2 1 A V block, and "maximal" stimulation resulted in higher degrees of A V dissociation Since the vagus nerve fatigues rapidly even at this frequency, periods of constant vagal activity, of necessity, were brief and often a progressive increase in the intensity of the stimulus was required to maintain a constant degree of A V delay Either the right or left vagus, or both simultaneously were employed in these experiments All hearts were driven at a constant rate before and during periods of vagal activation

Effect of section of the vagi Cutting both vagus nerves had no appreciable effect on excitability of the auricle as measured by the strength interval curve (Fig 47 C) Diastolic thresholds and the duration of the

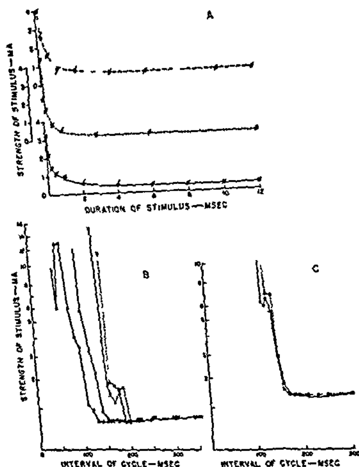


FIGURE 47 A. The lack of effect of vagal stimulation on auricular diastolic strength-duration curves obtained from three different dogs. The solid dots represent the control values in each animal. The other identifying marks represent thresholds during full vagal activation.

B Effect of vagal stimulation of various intensities on the strength interval curve of the auricle. The broken line (o———o) is the control weak (x——x) intermediate (•—•) and strong (Δ——Δ vagal stimulation

C Lack of effect of vagal section on cardiac excitability as indicated by lack of change in strength interval curves control (•—•) after vagal section (o———o)

absolute and relative refractory periods were similar before and after interruption of the vagi, as was the phase of supernormality when such was present These results are of interest in that they indicate an absence of tonic vagal effect on excitability in the preparation employed

Recovery of excitability In every case vagal activation shortened the absolute refractory period of the auricle, the degree of shortening being proportional to the strength of vagal stimulation (Fig 47 B) The magnitude of the change under strong vagal stimulation amounted to a 50 75% decrease from control values In typical experiments employing a test stimulus duration of 3 0 msec, the absolute refractory period shortened from 130 30 msec in one case, from 130 to 50 msec and from 100 to 50 msec in others When the test shock duration was increased to 12 msec,

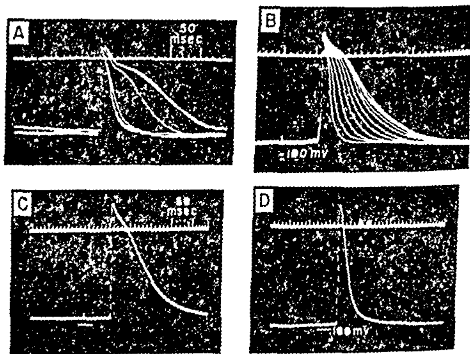


FIGURE 48 The effect of vagal stimulation on auricular transmembrane potentials In both A and B the longest lasting action potential is the control A shows the effects *during* vagal activity (changing from right to left) and B shows the changes after cessation of vagal stimulation (changing from left to right) C and D are records obtained from a single fiber of the isolated auricle before (C) and after (D) addition of acetylcholine in a concentration of 1 100 000 (Reproduced from Hoffman and Suckling 1953) (Retouched to show action potential upstrokes by dotted lines)

the duration of the absolute refractory period often fell to as little as 10 m.ec.

The total refractory period also shortened under vagal activation, but often not to the same extent as the duration of absolute refractoriness changes in the relative refractory period therefore were variable Weak vagal stimulation lowered the thresholds for extrasystoles during the relative refractory period stronger vagal activity restored excitability to normal resting levels during this interval of the cardiac cycle consequently shifting the relative refractory period to the left (Fig 47 B) The actual duration of relative refractoriness was most often increa ed by weak vagal activity at the expense of the absolute refractory period but under strong vagal timulation the duration of this period was definitely less than the control values

The transmembrane potentials of single fibers of the in situ dog auricle were also recorded to further clarify the effect of vagal stimulation on the excitability cycle of auricular muscle (Hoffman and Suckling 1953) As seen in the typical records reproduced in Figure 48-A when the peripheral trunk of either vagus nerve was stimulated and the heart rate kept constant by driving stimuli a rapidly progressive and dramatic change in the shape of the auricular action potential occurred Within a pace of 3 5 beats the time required for repolarization shortened to as little as 30 50 msec The recovery limb of the action potential developed a marked upward concavity with repolarization proceeding very rapidly at first and then more slowly as the resting membrane potential was approached. At the end of vagal timulation, as seen in Figure 48-B, the action potential returned to the control shape and duration.

These changes in the duration and time course of repolarization of the membrane of single auricular fibers graphically demonstrate the nature of the alterations underlying the recovery of excitability during vagal activity It is also interesting to note the clo.e correlation between the time course of repolarization of the single fiber and the course of recovery of excitability portrayed by the strength interval curves (Fig 47)

Dips and vulnerability Dips in the strength interval curve were less well defined under vagal influence and tended to shift to the left as the entire curve *was displaced in that direction* However the duration of the vulnerable period was invariably increased by vagal activity (see Chapter IX) and fibrillation thresholds were uniformly lowered Often fibrillation was the only response to threshold stimulation throughout the

major part of the relative refractory period Moreover, under maximal vagal effect suprathreshold stimuli could elicit fibrillation even late in diastole after the restoration of full excitability This contrasts markedly with the conditions obtaining in the absence of vagal activation (see Chapter VI)

When long lasting fibrillation or flutter occurred, vagal activity shortened the f f or p p cycle of these arrhythmias and often, when vagal stimulation ended, normal rhythm was restored The effects of vagal activity on vulnerability will be discussed more fully in conjunction with a consideration of the action acetylcholine

Resting excitability (diastolic threshold) Maximal stimulation of either or both vagus nerves had no effect on the level of resting excitability in auricular muscle The diastolic thresholds for stimuli ranging from 12 to 0 05 msec duration were unchanged by weak, intermediate or maximal vagal activity This constant level of resting excitability, clearly demonstrated in the strength duration curves of Figure 47 A, is in marked contrast to most experiments reported by others, wherein vagal stimulation or acetylcholine increased the rheobase of the turtle (Gilson, 1935), cat (DiPalma and Mascatello 1951) and dog (Andrus and Carter, 1930) hearts The absence of any change in diastolic thresholds during vagal stimulation observed in these experiments cannot be explained either by limitations of test shock duration or by ineffective nerve activation These interpretations are supported by experiments in which the effect of vagal stimulation on transmembrane potentials of the intact auricle were studied As can be seen in Figure 48, even strong vagal activity produced no appreciable change in the magnitude of the resting potential of auricular muscle although at times a maximum increase of 1 2 mv was noted, in association *with a slight increase in the rising velocity of the upstroke of the* action potential From these results little change in threshold would be expected (see Chapter II and V, and below) On the other hand, studies of the effect of acetylcholine on the transmembrane potentials of the isolated cat auricle (Burgen and Terroux, 1953) have revealed a definite increase in the resting potential associated with a change in the threshold requirement for stimulus current, similar investigations employing the embryonic chick heart (Fingl et al, 1952) have shown that acetylcholine decreased both the resting and action potential In both cases cited, the initial level of resting potential was quite low (60 mv and 45 mv respectively) This fact may explain the discrepancy between our observations on the effect

of the vagus on resting excitability and those of others It is quite possible that when the resting potential is abnormally low the addition of acetylcholine increases the transmembrane potential and thus changes the threshold to test shocks Observations of the effect of this agent on pacemaker activity in auricular muscle tend to support this concept (Brady and Hecht, 1954) When, on the other hand the initial level of membrane potential is close to the normal value vagal stimulation does not produce any appreciable change either in potential or threshold to test stimuli The difference between results obtained from studies of the dog auricle (Hoffman et al., 1952) and turtle or chick heart (Gilson, 1935 Fingl et al., 1952) may be true differences in the sensitivity of these separate species

Diastolic latency and conduction velocity When threshold test shocks were applied late in diastole, maximal vagal activation produced no change in latency of the response recorded 3 mm from the site of the test electrodes Diastolic conduction velocity on the other hand, was slightly increased by strong vagal stimulation (Hoffman et al., 1952) The conduction time from the driving electrode on the right auricle to a recording electrode on the left auricular appendage was decreased by 5-10 msec (a decrease of 10 to 20%) and changes of similar magnitude were obtained with recording electrodes closer to the drive site. This increase in conduction velocity cannot be accounted for on the basis of altered latency furthermore since the decrease in conduction time between each of several pairs of contiguous punctate bipolar electrodes was proportional to the distance separating them from the drive electrodes, the increased velocity of conduction cannot be ascribed to a shorter conduction path Finally the auricular strength interval curves clearly demonstrate that conduction both before and during vagal activity occurred in fully excitable tissue The claim that accelerated conduction during vagal stimulation is due to accelerated repolarization of the membrane (Garcia Ramos and Rosenblueth, 1947) is thus unsatisfactory since the vagal action results in faster conduction even in fully repolarized auricular tissue. Since accurate measurements of the rising velocity of the transmembrane action potential were not made the contribution of the slight increase observed cannot be evaluated in a quantitative manner However the direction of change in rising velocity would cause more rapid impulse propagation (Katz 1947) A slight increase in the magnitude of the "threshold potential" (see Chapter V) would have the same effect

but would most likely be associated with a measurable change in stimulus requirement Careful determinations of the effect of vagal activity on these two variables are therefore required before any conclusion can be reached

This observation of increased conduction velocity in auricular muscle at a time when A V conduction is markedly slowed or completely blocked emphasizes the specialized and unique nature of auriculo ventricular conduction Since the Purkinje fibers of the dog ventricle are completely unaffected by acetylcholine (Weidmann, 1953), the delayed A V conduction produced by vagal stimulation must occur at the junctional tissue or at the A V node itself

The monophasic auricular electrogram The monophasic electrogram of auricular muscle has been employed to demonstrate the effect of vagal activity or acetylcholine on the time course of repolarization (Hoffman et al, 1952) In such studies a large change in the magnitude of the action potential has been recorded Such a change is not revealed by the direct recording of transmembrane potential, this finding served as an excellent example of the ambiguity of tracings obtained by means of the former technique

Reversal of vagal effect Measurements made immediately after the end of vagal stimulation demonstrated that both the total and absolute refractory period of the auricle momentarily increased to a duration 5 10 msec greater than the control values, before returning to resting conditions The duration of the P R interval decreased below normal immediately after the cessation of vagal activity The same overshooting of the end point was demonstrated by the cycle length during fibrillation and flutter, during vagal stimulation this interval decreased below, and after the end of vagal activity it temporarily exceeded the control duration It is conceivable that this reversal of vagal effect on refractoriness and cycle length explains the occasional abolition of arrhythmias that can occur after the end of vagal stimulation

Comparison of the right and left vagus This series of experiments revealed no significant or consistent difference between the right and left vagus with respect to the changes produced in auricular excitability and conductivity

2 *THE ACTION OF VAGAL STIMULATION ON VENTRICULAR MUSCLE* Maximal stimulation of either vagus nerve, or of both simultaneously, at a frequency of 20/sec had no effect on either the excitability

or conduction velocity of the dog s ventricle when this chamber was driven at a constant rate

3 *THE EFFECTS OF ACETYLCHOLINE* The action of injected acetylcholine chloride on the excitability of the auricle and ventricle to testing stimuli was studied in several animals, the evanescent effect of this agent, however made complete studies of excitability by this technique impractical. Rather than either employ anticholinesterases or substitute long acting cholinergic agents for the acetylcholine subsequent studies in the intact animal were restricted to the recording of transmembrane potentials of single auricular and ventricular fibers before and during injection of varying quantities of acetylcholine chloride In addition the behavior of isolated preparations of auricular muscle and the isolated papillary muscle was observed in the presence of different concentrations of this agent and the changes in transmembrane potentials of single fibers of both tissues were recorded

Auricular membrane potentials When the transmembrane potential was recorded from a single fiber of the intact, driven auricle the injection of acetylcholine chloride into the external jugular vein resulted in changes similar to those produced by vagal stimulation with the sole exception that the onset of action was delayed and the duration of the resulting changes was prolonged Transmembrane potentials recorded from isolated fragments of auricular muscle exposed to concentrations of acetylcholine ranging from 5.5×10^{-10} to 11×10^{-2} M showed changes similar to those recorded from the in situ auricle during vagal stimulation. As shown in Figure 43-C D the total duration of the action potential decreased markedly the repolarization limb developed a marked upward concavity and the initial velocity of repolarization was greatly increased. In addition many preparations exhibited a slight increase in both the resting potential and the rate of rise of the action potential.

Regularly the effect of acetylcholine on the action potentials appeared very rapidly and there was no significant difference between records obtained at 1 5 and 20 minutes after addition of this agent to the bath. The lowest concentration of acetylcholine producing an important change in the auricular action potential was 5.5×10^{-8} M, while concentrations of above 5.5×10^{-2} created no further change in the shape or magnitude of the record.

Pacemaker activity and auricular arrhythmias In experiments performed in this laboratory with acetylcholine no records were obtained

from single fibers exhibiting pacemaker activity However, other investigators (Brady and Hecht, 1954, Hutter and Trautwein, 1955) have recorded the action of vagal stimulation on the slow depolarization which occurs preliminary to origin of a propagated action potential in pacemaker fibers These studies show that the vagal effect is to decrease the slope of the slow depolarization, or even to hold the membrane potential at a constant value The stoppage or slowing of heart rate when the vagus nerve is stimulated can be explained on the basis of this prevention or slowing of spontaneous depolarization in pacemaker tissue

On the other hand, administration of acetylcholine to many intact and isolated preparations resulted in the appearance of sustained spontaneous activity at extremely rapid rates (700 1500 beats/min) In the case of intact hearts, this activity was usually grossly irregular and disappeared quite rapidly In the isolated fragments of auricle, where a persistence of the acetylcholine effect was easily maintained, the arrhythmia was most often regular and of long duration It was found that in preparations

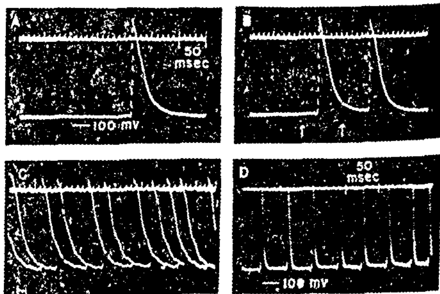


FIGURE 49 Production of arrhythmias in single auricular fibers treated by acetylcholine Response to a single stimulus shown in A The weak stimulus applied at a time indicated by second arrow in B gives an extra systole but a strong stimulus induces rapid multiple firing (C) Note extremely rapid rate of firing which sometimes results from this procedure (D) (Reproduced from Hoffman and Suckling 1953) (Retouched to show action potential upstrokes by dotted lines.)

of the latter type this same intrinsic tachycardia could regularly be produced by application of a suprathreshold stimulus at a certain instant during the repolarization phase of the action potential stimulation at other moments during recovery resulted only in the production of single extrasy toles. This sequence of events is shown in Figure 49

The records obtained during the intrinsic tachycardia described above are of interest in several respects First, they demonstrate that under the combined influence of acetylcholine and a rapid rate of intrinsic drive, auricular muscle is capable of complete repolarization within as little as 6-10 msec. This suggests that the fundamental mechanism underlying the depolarization and repolarization of auricular muscle may be quite similar to that present in skeletal muscle and that the long refractory period normally present in the auricle results from ome additional factor or mechanism that delays the repolarization process Secondly these records show that auricular muscle is capable of complete recovery at rates as high as 700-800/minute with no loss of resting potential or reversal, and even at twice this frequency there is only a small diminution in the resting potential and height of the action potential.

Simultaneous records of the action potential of a single auricular fiber and the local unipolar electrogram obtained before (Fig 50-A) and after (Fig 50-B C) the addition of acetylcholine and the production of this arrhythmia (Fig 50-D) clearly demonstrate the relationship between the rate of repolarization of auricular muscle and the timing and magnitude of the auricular T wave As repolarization occurs more rapidly under the influence of acetylcholine the T wave increases in magnitude and is inscribed progressively earlier until it blends with the deflection resulting from depolarization the record assuming a saw tooth configuration suggestive of the electrocardiogram during auricular flutter (Prinzmetal et al. 1952)

Ventricular membrane potentials Vagal stimulation as expected, did not change the action potential of single fibers of the intact dog ventricle as long as the heart was driven at a constant rate. Similarly doses of 1 5 ml. of acetylcholine solution (1 10 000), injected either into the external jugular vein, or directly into the cavity of the left ventricle, produced no change in either the resting potential, the height or rate of rise of the action potential, or the course of repolarization. In some cases measurements were obtained from the same fiber before and after the injection and in others several adjacent fibers were studied This lack of effect of

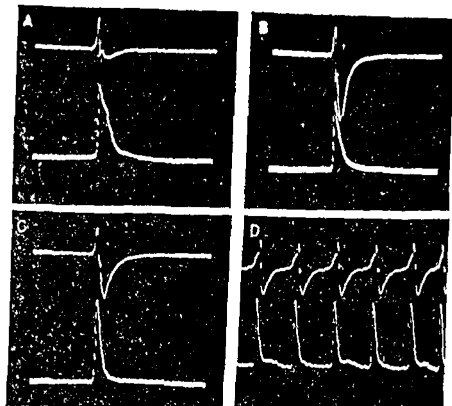


FIGURE 50 Relationship between auricular transmembrane potentials and the local electrogram See text for discussion (Reproduced from Hoffman and Suckling 1953) (Retouched to show action potential upstrokes by dotted lines)

high concentrations of acetylcholine on mammalian ventricular muscle was confirmed by studies employing the isolated papillary muscle preparation In these experiments only surface fibers were studied and intervals of up to five to ten minutes were allowed for any possible delay in diffusion of the acetylcholine to the membrane surface Results typical of this series of experiments are seen in Figure 51 Acetylcholine in concentrations from 5 5 x 10^{-12} to 5 5 x 10^{-4} M brought about no change, either in the size or shape of the action potential or in the magnitude of the resting potential The slope and duration of the three phases of repolarization remained unaltered Only with the highest concentrations employed (1 1 x 10^{-2} M) was there any modification of the membrane potentials, this consisted of a change in the slope of repolarization, the plateau tending to shorten and blend with the final phase of recovery Even when

this change did appear the total time required for repolarization was not decreased. At no time did acetylcholine induce either repetitive firing or arrhythmias in the isolated papillary muscle.

Additional confirmation of this demonstration that acetylcholine is without any effect on the time course of depolarization and repolarization of mammalian ventricular muscle is present in the work of Weidmann (1953) on the false tendon of the ventricle Here, too acetylcholine was found to exert no demonstrable effect on either the membrane action potentials or the rate of spontaneous activity However studies of the effect of this agent on the frog ventricle (Hoffman and Suckling 1952b) show a change in both the magnitude and duration of the transmembrane action potential. This observation emphasizes the differences that exist between various species in their response to acetylcholine, as has been mentioned previously

The mode of action of acetylcholine Any attempt to describe the possible mode of action of acetylcholine on the membrane phenomena and excit ability of auricular muscle is limited at the outset by the inadequacy of the information available. It is possible to assume that the basis of the membrane potential changes seen during activity in cardiac muscle is the same as that described for nerve and keletal muscle (see Chapter II)

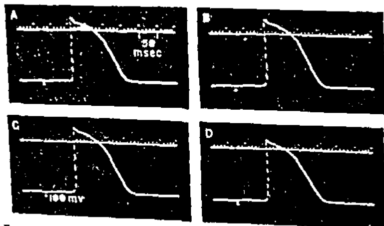


FIGURE 51 Lack of effect of acetylcholine on transmembrane action potentials of ventricular fibers. A—Control B—5.5 x 10^{-8} M C—5.5 x 10^{-6} M D—11.0 x 10^{-3} M acetylcholine (Reproduced from Hoffman and Suckling, 1953) (Retouched to show action potential upstrokes by dotted lines.)

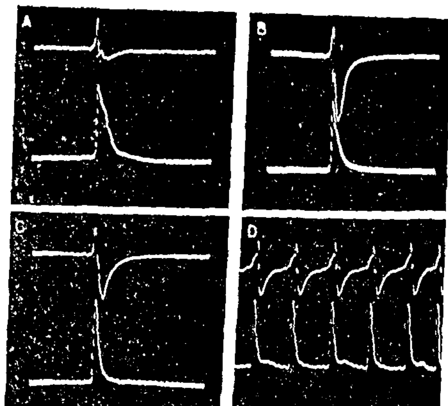


Figure 50 Relationship between auricular transmembrane potentials and the local electrogram See text for discussion (Reproduced from Hoffman and Suckling 1953) *(Retouched to show action potential upstrokes by dotted lines)*

high concentrations of acetylcholine on mammalian ventricular muscle was confirmed by studies employing the isolated papillary muscle preparation In these experiments only surface fibers were studied and intervals of up to five to ten minutes were allowed for any possible delay in diffusion of the acetylcholine to the membrane surface Results typical of this series of experiments are seen in Figure 51 Acetylcholine in concentrations from 5 5 x 10^{-12} to 5 5 x 10^{4} M brought about no change, either in the size or shape of the action potential or in the magnitude of the resting potential The slope and duration of the three phases of repolarization remained unaltered Only with the highest concentrations employed (11 x 10^{2} M) was there any modification of the membrane potentials, this consisted of a change in the slope of repolarization, the plateau tending to shorten and blend with the final phase of recovery Even when

lation and by acetylcholine This acceleration results at times in a completion of recovery within 10 msec.

3 The conduction velocity of a propagated response in resting auricular muscle is increased by both vagal stimulation and acetylcholine.

4. Vagal activity and acetylcholine greatly enhance the vulnerability of the auricle to flutter and fibrillation and often produce arrhythmias of this type.

5 Vagal activity has no effect on the excitability of the dog ventricle

6 Neither the resting potential nor the action potential of the dog auricle is decreased in magnitude by vagal stimulation but the duration of the action potential is greatly shortened.

7 The transmembrane potentials of the dog ventricle are not affected by acetylcholine or vagal timulation.]

4. *STIMULATION OF CARDIAC SYMPATHETIC NERVES* The techniques followed in stimulating the cardiac sympathetic nerves were similar to those employed in studies of vagal activity The major cardiac nerves, both left and right, were isolated and cut and the distal segments placed in moist chamber electrodes. The stimuli used were sinusoidal pulses at a frequency of 16 per second. In various experiments either the right or left or both nerves were brought into action by means of supramaximal stimuli for brief periods ranging from 30 seconds to 2 minutes duration At times the right or left stellate ganglia or the thoracic autonomic chains were similarly stimulated In each case, an attempt was made to sever all connections other than those running to the cardiac plexi.

In all experiments involving stimulation of cardiac sympathetics the vagi were sectioned high in the neck to prevent reflex activation and the heart was driven at a constant rate before and during nerve stimulation whenever tests of thresholds and refractoriness were made. The driven rate adopted was 200/minute to prevent escape from the drive stimuli during sympathetic activity In a number of experiments the S A node was not inactivated thus the effect of sympathetic stimulation on the rate of nodal impulse formation could be evaluated Several pairs of contiguous bipolar electrodes on both auricle and ventricle permitted measurements of intra auricular intra ventricular, and auriculo-ventricular conduction velocity Determinations of thresholds and the boundaries of the refractory periods were made in the usual manner When either the right or left cardiac nerves were stimulated the following changes were noted.

If this is true, then depolarization of the cardiac muscle membrane is associated with an increase in sodium permeability of the cell membrane and an inward Na^+ current and repolarization with a rise in potassium permeability and outward K^+ current (the uncertainty of changes of K^+ flux have been discussed in Chapter V)

If we accept this hypothesis, one can suggest a possible mode of action of acetylcholine on auricular tissue There is evidence from several types of experiments (Burgen and Terroux, 1953a,b, Holland et al, 1952, Holland, 1954, Hutter and Trautwein, 1955) indicating that acetylcholine increases the permeability of the resting membrance to K^+ Such an increase in the resting K^+ conductance could be at least partly responsible for the slight observed increase in resting potential that follows vagal activity and would also account for the slowing of pacemaker activity that has been described Thus it is possible that acetylcholine increases the rate of repolarization in auricular fibers by altering the permeability of the membrane to potassium If such a change in permeability does occur, however, it must be of a different nature than that produced at the motor endplate by the same agent (Fatt and Katz, 1951, Nastuk, 1953), in skeletal muscle the action of acetylcholine at the endplate causes a pronounced depolarization—the endplate potential—and also a significant local decrease in the height of the transmembrane action potential

On the other hand the time course of repolarization in auricular muscle is normally so different from that of skeletal muscle that some different mechanism may be operative If such is the case, acetylcholine may act directly on this process The observation that fluoride (Hoffman and Suckling, 1952b) and high calcium concentrations (Chapter 10) can produce similar marked acceleration of the repolarization process in the auricle demonstrates that the effect of acetylcholine is not unique

The lack of sensitivity of ventricular muscle to acetylcholine is most likely due to the fact that cholinergic nerve endings are not present in this tissue and thus the membrane, like that of skeletal muscle distant from the neuromyal junction, does not possess appropriate *receptors*

Summary The more important actions of acetylcholine, whether injected or liberated by nerve action, on cardiac excitability may be summarized as follows

1 The level of resting excitability of auricular muscle is not changed by maximal vagal activity

2 Repolarization of the auricle is greatly accelerated by vagal stimu

The technique of single fiber recording from the intact ventricle was employed in a number of experiments to verify these results Stimulation of either sympathetic chain failed to modify the action potential of single ventricular fibers to any appreciable degree with respect to either magnitude or total duration

General considerations While the acceleration of heart rate and con duction velocity provided conclusive evidence that at least some of the sympathetic nerves to the heart had been activated in these experiments the minimal and seemingly unpredictable changes in resting excitability and total duration of the period of subnormal excitability were surpris ing Two additional groups of experiments were performed to clarify the results discussed above First, the effect of hepatic nerve stimulation was studied since these fibers are known to liberate quantities of adrenergic mediator adequate to influence both cardiac muscle and other distant effectors Subsequently the effects of equimolar quantities of injected l-epinephrine and l nor-epinephrine were investigated

5 *HEPATIC NERVE STIMULATION* The hepatic nerves were freed from the hepatic artery cut centrally, and enclosed in a moist-chamber electrode The stimuli were similar in shape and frequency to those de scribed previously Supramaximal stimulation of the nerve plexus produced a marked rise in blood pressure and heart rate and in addition brought about a considerable change in the level of resting excitability of the ventricle As shown in Figure 52 soon after the onset of stimulation there was an abrupt and marked fall in the diastolic threshold, often amounting to a change of 30-40% and lasting 1 2 minutes Subsequently, following termination of the nerve activity the threshold rose considerably above

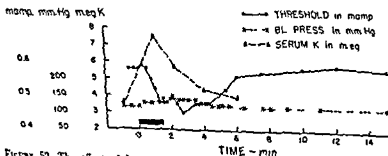


FIGURE 52. The effect of hepatic nerve stimulation on diastolic threshold, systolic blood pressure and serum potassium. Duration of stimulation indicated by solid bar

Electrocardiographic changes a) Heart rate In undriven preparations the rate of impulse formation was markedly increased, similarly in driven hearts the nerve activation accelerated the intrinsic pacemaker so that the heart often escaped from the drive stimuli and beat in response to a rapid intrinsic rhythm

b) Conduction velocity Both intra auricular and intra ventricular conduction velocity were increased slightly by nerve stimulation This change was manifested by both a decrease in interelectrode conduction times and a decrease in the total duration of the P wave and QRS complex of the limb lead electrocardiogram Auriculo ventricular conduction was accelerated more markedly and resulted in a significant decrease in the PR interval of the electrocardiogram

Although the R T segment of the electrogram demonstrated only minor changes during nerve activity, the shape and voltage of the T deflection were clearly altered, the T becoming taller and more peaked in all cases

c) Mechanical effects In most instances stimulation of the cardiac nerves resulted in a moderate increase in systemic blood pressure, much more marked, however, was the increase in vigor of contraction of the ventricular muscle

Resting excitability The change in resting excitability produced by stimulation of the cardiac sympathetic nerves was determined both by measuring the threshold late in diastole with a stimulus of fixed duration and also by obtaining a complete strength duration curve before, during and after nerve activity In most hearts sympathetic activity produced a minimal lowering of auricular and ventricular diastolic thresholds Often this lowering disappeared during continued stimulation and thresholds rose to levels slightly above the control level, returning to normal only after the nerve activity had been terminated At other times, however, stimulation of the cardiac nerves brought about either no change in resting excitability or an immediate slight increase in the threshold above resting values These changes were all revealed more clearly by means of a single, short duration stimulus than by determination of the entire strength duration curve

The duration of refractoriness Stimulation of the cardiac sympathetic nerves produced only slight alterations in duration of the total refractory period of ventricle and auricle This interval of the cardiac cycle increased in some experiments and decreased in others, in no instance was the magnitude of change greater than 10 15 msec

The technique of single fiber recording from the intact ventricle was employed in a number of experiments to verify these results Stimulation of either sympathetic chain failed to modify the action potential of single ventricular fibers to any appreciable degree with respect to either magnitude or total duration

General considerations While the acceleration of heart rate and conduction velocity provided conclusive evidence that at least some of the sympathetic nerves to the heart had been activated in these experiments, the minimal and seemingly unpredictable changes in resting excitability and total duration of the period of subnormal excitability were surprising Two additional groups of experiments were performed to clarify the results discussed above First, the effect of hepatic nerve stimulation was studied since these fibers are known to liberate quantities of adrenergic mediator adequate to influence both cardiac muscle and other distant effectors Subsequently the effects of equimolar quantities of injected l-epinephrine and l nor-epinephrine were investigated

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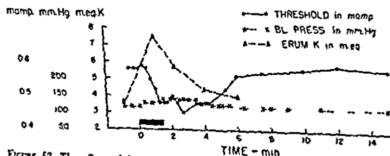


FIGURE 52. The effect of hepatic nerve stimulation on diastolic threshold, systolic blood pressure and serum potassium. Duration of stimulation indicated by solid bar

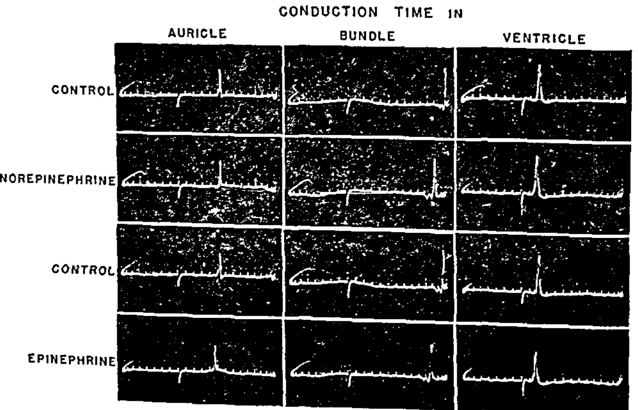


FIGURE 53 Electrograms recorded with punctate bipolar electrodes demonstrating the effect of equimolar amounts of l-epinephrine and l nor-epinephrine on conduction velocity in the dog's heart. Time is indicated in 10 (small pips) and 50 (large pips) msec intervals Drive stimulus artefact is downward (Reproduced from Siebens et al., 1953) Conduction time measured from drive artefact to electrogram complex

resting values and returned to the pre-stimulation level only after several minutes. Simultaneous with the fall in threshold there was a moderate decrease in the duration of the total refractory period

6 *SYMPATHOMIMETIC AMINES* Following establishment of control values for threshold and refractoriness freshly made solutions of either l-epinephrine or l nor-epinephrine were injected via the femoral or external jugular vein from a constant speed mechanical syringe A 1 25 000 dilution of the chloride salt of either l-epinephrine or l nor-epinephrine was employed in most cases, in some experiments l nor-epinephrine bitartrate 1 16 000 or d l nor epinephrine Cl 1 12,500 was substituted for the above Both the total volume and the rate of injection were varied in different experiments (actual values will be specified whenever necessary) The effects of such injections can be summarized

Conduction velocity Conduction velocity was measured in auricle and ventricle by recording the elapsed time between the application of the driving stimulus to either chamber and the arrival of the propagated impulse at a distant pair of recording electrodes applied directly to the same chamber A V conduction velocity was determined in the usual manner The effect of equimolar doses of l-epinephrine and l nor-epinephrine on conduction velocity is demonstrated in Figure 53 While both agents increased the rate of impulse propagation in auricle, A V bundle and ventricle the effect of l epinephrine was uniformly greater than that of l nor-epinephrine. This difference was particularly marked in the case of A V conduction. Up to a maximum, the magnitude of change in conduction velocity varied with the rate of administration in most experiments an injection of 4.0 ml. at 2ml./minute produced maximal acceleration of impulse propagation

Heart rate and rhythmicity Both l-epinephrine and l nor-epinephrine produced marked increases in the rate of spontaneous impulse formation in the S A node of undriven hearts. In driven hearts when the S A node was crushed both agents similarly increased the intrinsic rate and, with large concentrations both produced ectopic ventricular rhythms which usually commenced one minute after the onset of injection and lasted considerably longer than the duration of drug administration In no case did *spontaneous ventricular* fibrillation occur

While the relative potency of each agent with respect to increasing heart rate varied from dog to dog l nor-epinephrine usually caused somewhat faster rates than did epinephrine

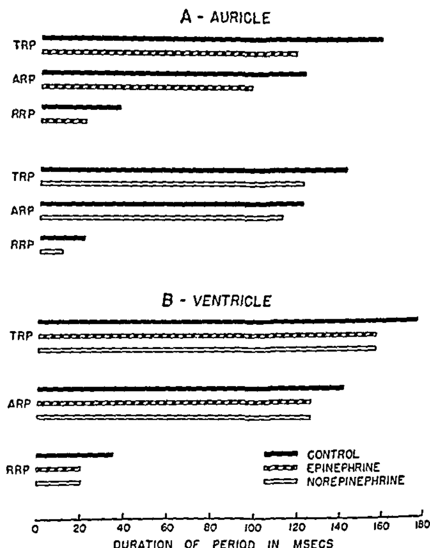


FIGURE 54 The effect of equimolar amounts of l epinephrine and l nor-epinephrine on the duration of refractoriness of the dog's heart TRP—total refractory period ARP—absolute refractory period, RRP—relative refractory period

A. Comparison of epinephrine and nor-epinephrine on the auricle Note slight change in control values between tests

B Comparison of epinephrine and nor-epinephrine on the ventricle (Reproduced from Siebens et al 1953)

The duration of refractoriness In the majority of experiments the refractory periods of both the auricle and ventricle were shortened by l-epinephrine and l nor-epinephrine as demonstrated in Figure 54. In either chamber both the absolute and relative refractory periods were decreased to a similar extent by equimolar doses of the two agents employed Noteworthy is the fact that in no case was the degree of shortening particularly marked the average change in the duration of either the relative or absolute refractory period of auricle or ventricle amounting to 10-15 msec.

Isolated papillary muscles and isolated auricle preparations were employed to study the effect of l-epinephrine on the duration of the action potential of single fibers The microelectrode records of the transmembrane potentials shown in Figure 55 demonstrate that in typical preparations of auricular tissue this agent definitely increased the rate of repolarization and shortened the total action potential duration In many

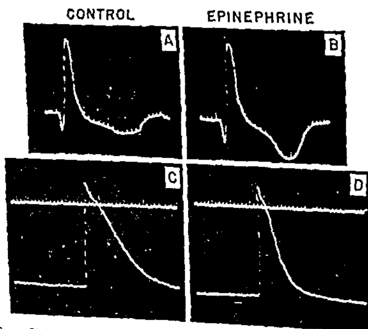


FIGURE 55 The effect of epinephrine on the ventricular unipolar electrogram (A and B) and on the transmembrane action potential of a single auricular fiber (C and D) Time marks in 10 and 50 msec. intervals. (Retouched to show action potential upstrokes by dotted lines.)

experiments, however, the degree of shortening was less than that shown Similarly, in the papillary muscle of the dog's right ventricle l-epinephrine likewise produced a slight decrease in the total duration of the action potential In neither tissue, however, were significant changes in resting potential produced by the concentrations of sympathomimetic amine employed (Figure 55) These results are in general agreement with the studies of Fingl et al (1952), performed on the chick embryo and frog heart. Noteworthy is the fact that the changes in duration of the refractory period produced by l epinephrine and l nor epinephrine are in no way comparable to the dramatic decrease in duration of auricular refractoriness that results from vagal activity or the marked change in duration of the refractory period of ventricular muscle that accompanies alterations in heart rate

In a few dogs no measurable decrease in the duration of the total period of subnormal excitability was elicited by administration of either agent. However, a significant prolongation of this interval of the cardiac cycle was not found following injection of the sympathomimetic amines The unipolar electrogram revealed T wave changes similar to those produced by sympathetic nerve stimulation, consisting of an increase in voltage and peaking of this deflection with little concomitant change in the duration of the R T interval (Figure 55)

Resting excitability The observed changes in diastolic thresholds resulting from the administration of l epinephrine and l nor-epinephrine varied with the rate and volume of the injection Small doses of either agent, administered at a rate of approximately 0 5 1 0 ml /min , produced a transitory drop in threshold of both auricle and ventricle to levels 10 25% below the control In the auricle this phase of increased excitability lasted for 1 2 minutes, in the ventricle the duration was somewhat greater, the average time ranging from 3 4 and occasionally reaching a maximum of 5 minutes The duration of this stage of increased excitability seemed to be independent of the duration of the injection Thus, even though the administration of the sympathomimetic agent continued for 10 15 minutes, the threshold returned to control values within the usual period of time Larger amounts of either agent, injected at rates of 2-4 ml /min , produced a greater decrease in threshold (to levels 25 50% of the control) of approximately the same duration, but following this the thresholds increased to and then exceeded the control by as much as 50% This phase of decreased excitability lasted for 5 30 minutes, and appeared irrespective of whether the injection of sympathomimetic agent was ended during the stage of

enhanced excitability or continued for several minutes after maximum drop in threshold had been attained. Examples of these changes in auricular excitability following both l-epinephrine and l nor-epinephrine are seen in Figure 56 similar alterations in ventricular threshold are seen in Figure 57

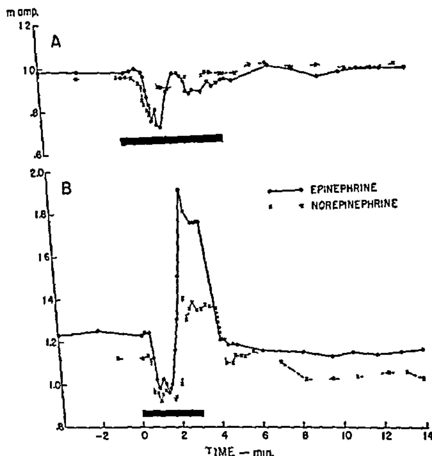


Figure 56 The effect of l-epinephrine and l nor-epinephrine on diastolic thresholds of the dog's auricle. 6.5 ml. of a 1.25 000 dilution of either agent injected during interval indicated by solid bar

Ordinate—threshold in ma. abscissa—time in minutes prior to and following start of injection. (Reproduced from Siebens et al., 1953)

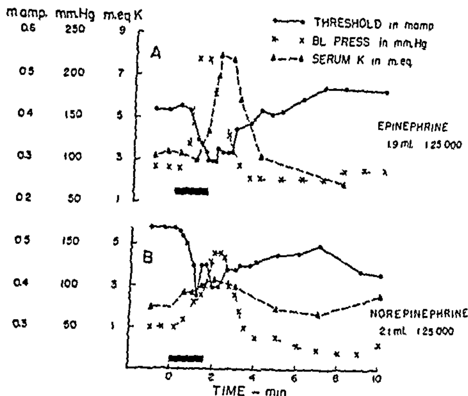


FIGURE 57 The effect of l-epinephrine (A) and l nor epinephrine (B) on ventricular diastolic thresholds, serum potassium concentration and systolic blood pressure Time of injection indicated by solid bar (Reproduced from Siebens et al., 1953)

When equimolar doses of l epinephrine and l nor epinephrine were compared in the same animal, the former usually produced a slightly greater change in excitability of both auricle and ventricle regardless of the sequence of administration of the two agents (Siebens et al, 1953) Furthermore, when the effects of either drug on the auricle and ventricle of the same animal were compared, it was found that the relative sensitivity of each chamber to epinephrine or nor epinephrine might be quite different Table 5 summarizes the early changes in auricular and ventricular excitability produced by both l epinephrine and l nor epinephrine in several representative experiments When the injection of either l epinephrine or l nor epinephrine was extremely slow (0 1 0 25 ml /min), the changes in resting excitability were either absent or extremely slight, amounting to a drop in threshold of no more than 10%

Vulnerability to fibrillation Both l-epinephrine and l nor epinephrine

produced a marked increase in the susceptibility of ventricular muscle to fibrillation induced by single suprathreshold test hocks applied during the vulnerable period This enhanced vulnerability was of brief duration, coincided temporally with the lowering of diastolic thresholds and was often followed by a phase of decreased susceptibility to fibrillation of somewhat greater duration The effect of these two agents on the susceptibility of auricular muscle to fibrillation was less clear-cut. These problems are discussed in Chapter IX.

7 *BLOOD PRESSURE CHANGES AND EXCITABILITY* A causal relationship between the changes of excitability and the elevation of blood pressured produced by both l-epinephrine and l nor-epinephrine was made unlikely by the observation that similar marked elevations of blood pressure, produced by aortic occlusion gave rise to no change in excitability of either auricle or ventricle The similar absence of any alteration in thresholds of the dog ventricle in spite of large variations in intraventricular pressure has been reported previously (Woske, et al., 1953)

COMPARISON OF CARDIAC AND HEPATIC NERVE STIMULATION AND THE ACTION OF POTASSIUM CHLORIDE AND SYMPATHOMIMETIC AMINES ON EXCITABILITY OF THE HEART

These studies demonstrate several important points First, the actions of injected l-epinephrine and l nor-epinephrine are remarkably similar with respect to their effect on excitability rhythmicity and refractoriness of auricular and ventricular muscle *Furthermore* hepatic nerve stimulation by means of supramaximal shocks is likewise quantitatively and qualitatively similar in effect to the administration of these agents in large amounts On the other hand, activation of the cardiac sympathetic nerves, while it does result in alteration *in rate* rhythm, conduction velocity, and force of contraction does not produce comparable changes either in the level of resting excitability or in the duration of the total refractory period These observations suggest that some additional factor or factors are operative in the case of hepatic nerve stimulation and administration of sympathomimetic amines

It is known that the injection of either epinephrine or to a lesser extent, nor-epinephrine produces a marked biphasic change in serum potassium concentration In addition excitability and resting membrane potential are strongly influenced by the concentration of extracellular K^+ Because of this the relationships between alterations in threshold and changes in serum

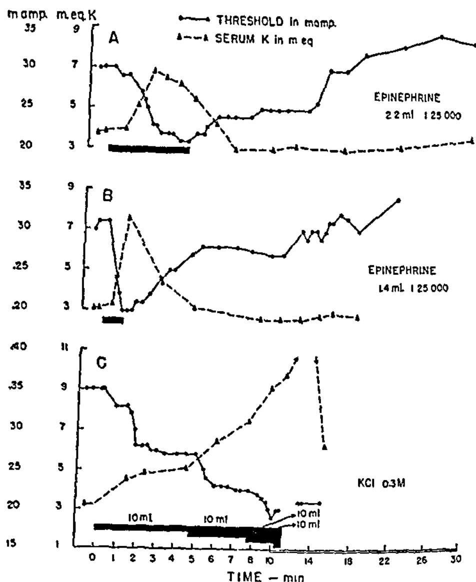


FIGURE 58 The effect of slow (A) and rapid (B) injection of l-epinephrine on ventricular diastolic thresholds and serum potassium concentration C—The effect of injecting 0 3 M KCl at increasing rates on ventricular diastolic thresholds and serum potassium concentration Volume injected at each rate indicated in figure (Reproduced from Siebens et al 1953)

K^+ concentration were studied both following the injection of sympathomimetic amines and following stimulation of sympathetic nerves

Serum potassium concentration was determined by means of a flame photometer employing external standards. Heparinized samples of blood were drawn from the right common carotid artery through an indwelling polyethylene catheter before during and at various intervals after each injection Blood collected in the catheter was washed out before the sample to be analyzed was taken, this total procedure required approximately 20 seconds.

TEMPORAL RELATIONSHIP BETWEEN CHANGES IN K CONCENTRATION AND RESTING EXCITABILITY In all experiments (Figure 57 A) when l-epinephrine was injected the rapid fall in the ventricular diastolic threshold was accompanied by a simultaneous increase in serum potassium to over twice the control value and the maximum changes in both variables were nearly simultaneous Also, the return to normal of excitability and serum potassium concentration occurred at approximately the same time Similarly whether epinephrine was injected at a slow or rapid rate (Figure 58 A B), the drop in threshold paralleled the rise in serum K On the other hand the return to normal of *these two variables was not simultaneous and the period of* subnormal excitability was distinctly out of phase with the fluctuations in serum K In this and other experiments potassium levels would often drop below control values before the threshold returned to normal and usually the period of subnormal excitability lasted considerably longer than did the subnormal serum potassium concentration

Following injection of a similar amount of l nor-epinephrine (Figure 57 B) although the magnitude of threshold change and the temporal relationship of this change to alterations in serum potassium were the same as before the increase in serum potassium concentration was relatively slight.

The effects of hepatic nerve stimulation on both the level of resting excitability and the serum potassium concentration were quantitatively and qualitatively similar to those of injected l-epinephrine (Figure 52) The early fall in threshold was accompanied by an abrupt rise in serum K^+ and the peak changes were approximately simultaneous Both threshold and serum K concentration overshot the control values on returning to normal The periods of low serum potassium and subnormal excitability were not necessarily coextensive. Activation of the cardiac sympathetics on the other hand produced no significant change in serum potassium levels.

TABLE 5—*Comparison of Activity of l epinephrine and l nor-epinephrine in Lowering Diastolic Thresholds*

Experiment	Date	Sequence of Administration	Total Dose	Rate of Injection	Maximum Decrease in Threshold
Ventricle	10/1/52	Epinephrine	5 ml	1 ml /min	25%
		Epinephrine	6 ml	"	28%
		Nor epinephrine	3 ml		14%
		Epinephrine	3 ml	"	27%
		Nor-epinephrine	6 ml	"	20%
	3/20/52	Nor epinephrine	1 ml	0 5 ml /min	25%
		Epinephrine	1 ml	"	27%
		Epinephrine	1 5 ml	1 0 ml /min	53%
		Nor epinephrine	1 5 ml		50%
	2/3/53	Epinephrine	1 9 ml	1 ml /min.	44%
		Nor-epinephrine	2 1 ml		49%
Auricle	2/7/52	Nor epinephrine	4.25 ml	1.5 ml./min	10%
		Epinephrine	4 25 ml	"	20%
	3/25/52	Epinephrine	7 ml	1 5 ml./min	23%
		Nor-epinephrine	7 ml		31%
	4/22/52	Nor-epinephrine	6 75 ml	1 5 ml./min	20%
		Epinephrine	6 75 ml.		21%
		Epinephrine	6 0 ml	2 0 ml /min	22%
		Nor-epinephrine	6 0 ml	"	18%

EFFECT OF INJECTED KCl A further study of the possible inter relationship between changes in serum potassium concentration and resting excitability was made by injecting KCl intravenously in quantities sufficient to give increments in serum concentration similar to those produced by epinephrine, and determining the concomitant change in level of resting excitability When this was done, it was seen that, for a given elevation of serum K^+, the magnitude of the threshold change was the same as that accompanying injection of the sympathomimetic amine This effect is demonstrated in Figure 58 C *Only when the serum potassium concentration exceeded 9 mEq /l* did thresholds begin to increase usually at this level A V block and ventricular extrasystoles precluded further testing of resting excitability

EFFECT OF HEPATECTOMY Since it was anticipated that hepatectomy would greatly decrease the change in serum potassium caused by

epinephrine threshold changes resulting from the injection of this agent were determined before and after removal of the liver in 10 dogs

Hepatectomy was accomplished in the following manner after ligation of the hepatic artery, the portal vein was cannulated and the blood flow diverted to the left external jugular vein Subsequently, a plastic cannula was inserted into the inferior vena cava in such a fashion that the ends of the cannula extended 1 2 cm above and below the liver The vena cava was then tightly ligated around this cannula close to its two ends In several experiments after the liver had been excluded from the circulation in this manner the entire organ was extirpated

Six experiments were satisfactory in that, in spite of the surgical trauma resulting from both thoracotomy and laparotomy, adequate tests

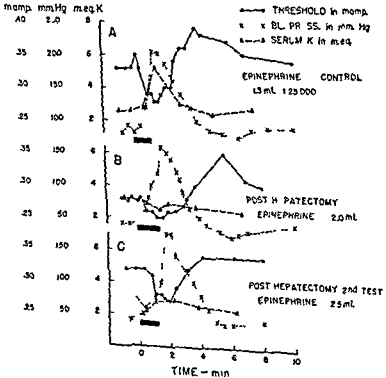


FIGURE 59 The effect of hepatectomy on the changes in ventricular diastolic thresholds serum potassium concentration and blood pressure produced by l-epinephrine (Reproduced from Siebens et al, 1953.)

could be performed Results typical of four of these experiments are seen in Figure 59 In these animals the control dose of l epinephrine produced the usual marked drop in threshold and simultaneous rise in serum potassium Following hepatectomy a slightly larger dose of epinephrine gave a diminished threshold response, but no increase in serum potassium concentration Finally twice the control amount of epinephrine produced a change in threshold comparable to the control curve, but again caused no elevation in serum potassium In the other two experiments, hepatectomy resulted in a smaller decrease in the threshold response to epinephrine, however, in these animals slight elevations in serum potassium level (amounting to 20 50% of the control response) still resulted from epinephrine administration In contrast to the above, hepatectomy did not alter the lowering of threshold that resulted from the injection of l nor-epinephrine and produced only a slight decrease in the phase of subnormal excitability

EVALUATION OF RESULTS A consideration of the results obtained on stimulation of the cardiac and hepatic nerves and on administration of sympathomimetic amines permits certain conclusions concerning the action of these agents on cardiac muscle The observation that l epinephrine and l nor epinephrine have qualitatively and quantitatively similar actions on cardiac excitability is of considerable interest, in view of the fact that they differ markedly in their ability to elevate blood glucose and potassium levels and also in their actions on other effectors such as uterine and intestinal smooth muscle (Gaddum et al, 1949) and the nictitating membrane (Fleckenstein and Burn, 1953) The great difference in the elevation of serum K^+ concentration that follows administration of these two amines in doses producing similar changes in excitability, and the diminished effectiveness of epinephrine following hepatectomy suggests that, mole for mole, nor epinephrine is more potent with respect to eliciting *changes in cardiac excitability*

The demonstration that stimulation of the hepatic nerves produces changes in both the level of resting excitability and serum potassium identical to those resulting from the usual doses of l epinephrine indicates that the quantities employed are within a reasonable range and that the excitability changes produced are similar to those that result from the liberation of sympathetic mediators from intrinsic sources

In light of these considerations and also the probability that the major mediator at the postganglionic terminals of the cardiac sympathetic nerves

is nor-epinephrine it is difficult to explain the slight changes in resting excitability and duration of refractoriness that result from activation of these nerves It seems that the predominant effect of stimulation of the cardiac nerves is on the rate of impulse formation in the S A and A V nodes (Hutter and Trautwein, 1955) and on conduction velocity in special ized tissues. This suggests that the concentration of sympathetic endings is greater around these structures than elsewhere in the auricle and ventricle an observation supported by histological studies. Since at no time was more than a part of the total sympathetic supply to the heart activated and since there is evidence that the density of endings in non specialized cardiac muscle is low it is not surprising that stimulation of the cardiac nerves failed to produce a high enough concentration of mediator throughout the heart to greatly modify resting excitability or refractoriness Such changes as do occur, however are similar to those produced by injections of the sympathomimetic amines Furthermore it is certain that the elevation of serum K is not present during stimulation of the cardiac nerves and thus a lesser change in excitability is to be expected. The relationship between serum potassium and excitability is further discussed in Chapter X.

SUMMARY The major effects resulting from stimulation of sympathetic nerves or injection of sympathomimetic amines can be summarized as follows

1 Injection of either l-epinephrine or l nor-epinephrine results in marked tachycardia in the dog heart when both vagus nerves are sectioned There is little difference between these agents with respect to the maximum rate produced or the occasional appearance of ectopic ventricular rhythms Stimulation of the cardiac or hepatic nerves has similar effects on the rate of impulse formation but fails to elicit ectopic rhythms

2. Both l-epinephrine and l nor-epinephrine increase conduction velocity in the auricle A V tissue and ventricle. The effect of epinephrine is more marked in this respect, especially on A V conduction velocity The magnitude of change is similar to that produced by stimulation of the cardiac sympathetic nerves.

3 The level of resting excitability of both auricular and ventricular muscle is strongly influenced by injected sympathomimetic amines and the direction and magnitude of change is related to the rate of drug administration The actions of l-epinephrine and l nor-epinephrine on resting excitability are qualitatively and quantitatively similar Hepatic

nerve activation has an effect indistinguishable from that of the injected amine, stimulation of the cardiac sympathetics, on the other hand, produces little change in the level of resting excitability

4 The changes in the duration of refractoriness produced by epinephrine, nor epinephrine and hepatic nerve stimulation consist of a moderate shortening of the total refractory period Cardiac sympathetic activity has even less effect on the duration of the period of subnormal excitability

5 The lowering of the diastolic threshold produced by either epinephrine, nor epinephrine or hepatic nerve activation is associated with prominent changes both in vulnerability to ventricular fibrillation and in the concentration of serum potassium All three of these variables tend to undergo a biphasic alteration that follows a typical time course The changes in vulnerability are further discussed in Chapter IX.

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IX Fibrillatory and Antifibrillatory Agents

A discussion of spontaneous and induced defibrillation Consideration of the effects and mode of action of common antifibrillatory agents and substances which tend to produce arrhythmias The role of drugs in the production and treatment of auricular and ventricular fibrillation

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IN A PRECEDING CHAPTER the nature and etiology of fibrillation and vulnerability of the heart were discussed in some detail Disease cardiac injury the stimulating effects of drugs anesthetics and physical forces acting on the heart, all too frequently produce fibrillation of the auricles and even the ventricles The occurrence and the possibility of the occurrence of these catastrophic happenings have aroused and maintained interest in the nature and cause of cardiac fibrillation Much effort has been devoted to the problem of preventing fibrillation and other cardiac arrhythmias and to the discovery of means of stopping fibrillation once it has developed

Studies of the effect of various agents on the auricular arrhythmias can be accomplished without difficulty in most instances since in the dog disturbances of auricular rhythm are self limiting Even when an occasional fibrillation or flutter does eventuate the hemodynamic effects are slight moreover in every case normal activity can be restored by means of simple measures such as vagal stimulation or direct faradization of the auricular appendage. Furthermore neither the arrhythmias themselves nor the defibrillation procedures mentioned have any persistent effect on the subsequent excitability of the auricular muscle a brief period of rest allows full restoration of normal values When the vulnerability of the ventricle is under investigation, on the other hand a problem of much greater difficulty is encountered Should fibrillation occur, rather drastic countermeasures are required before regular coordinated activity is resumed and these must be executed quickly or irreversible changes will occur It is necessary because of these temporary effects of fibrillation in the myocardium to evaluate the effect of repeated fibrillation and defibrillation on various parameters of auricular and ventricular excitability and response before detailed studies of the actions and effects of fibrillatory and antifibrillatory agents can be discussed

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restored but usually this procedure leaves the heart in rather poor condition and fibrillation is likely to again ensue

Sudden application of cold (Porter 1898 Garry 1924 Hoff and Stansfield 1949), injections of adrenaline adenosine triphosphate quinidine and numerous other drugs (Kerr and Bender 1921, Garry 1924 Wanger and Blackberg 1932 Schwartz et al, 1949, Dawes 1952 Hecht et al 1953 Durken et al, 1955) may in some instances and under certain circumstances abolish fibrillation. Sudden cooling of the heart does prolong refractoriness, reduces excitability and throws the whole heart into a more uniform state Slow cooling or localized cooling increases the heart's vulnerability to fibrillation (see Chapter VII) Adrenaline when on rare occasions it defibrillates the heart, presumably does so either by its excitatory action on the pacemaker tissue and conduction or by its postexcitatory depressant action (Siebens et al., 1954) The point to emphasize is that just as disorganization can be created by a variety of influences acting either on the excitatory process, conduction or the duration of the refractory periods it also seems that defibrillation may result from modification of these three processes It should also be pointed out that factors other than those mentioned here and which cannot be assayed by the techniques thus far employed are also involved in fibrillation. This latter point is emphasized by the studies of the mode of action of antifibrillatory drugs One point is relatively clear and that is that these methods of defibrillation (use of cold adrenaline quinidine, ATP, KCl, etc.) are either unusable under most circumstances or are so highly unsuccessful that consideration of them from other than a theoretical viewpoint is unwarranted

DEFIBRILLATION BY ELECTRICAL COUNTERSHOCK Ventricular fibrillation can be very effectively terminated by the application of strong electric shocks Alternating or direct current pulses or even condenser discharges will stop fibrillation (Lape et al., 1952 Wiggers 1940 1953 Kouwenhoven and Milnor 1954) Although the fact that ventricular fibrillation can be abolished by *direct application* of electric current was observed as long ago as 1775 (Abildgaard, 1775), the first experimental studies were those of Prevot and Battelli (1899 1900) It was not until the more recent work of Hooker et al., (1933) Ferris et al (1936), Wiggers and his associates (1930 1940 1953) demonstrated the reliability and effectiveness of electrical countershock in abolishing fibrillation that much use of this procedure was made Countershock as an emergency

DEFIBRILLATION—THE TERMINATION OF DISORGANIZED ACTIVITY OF THE HEART

SPONTANEOUS DEFIBRILLATION Both auricular and ventricular fibrillation generally terminate spontaneously in the hearts of the smaller mammals, amphibia and reptiles but in the larger mammals and in man ventricular fibrillation is almost invariably fatal The hearts of small dogs do occasionally show spontaneous defibrillation and temporary brief periods of fibrillation have been observed in man (Beck et al, 1947) The larger the heart the more readily can long lasting fibrillation be produced and the more difficult is defibrillation (Erlanger, 1912, Rijlant, 1945) The auricles of larger animals escape from fibrillation more readily than does the ventricle and this is another indication that the area and mass of tissue is important to the factors maintaining the condition

DEFIBRILLATION BY METHODS OTHER THAN ELECTRICAL COUNTERSHOCK Numerous means have been employed to defibrillate the heart If they are to be successful the methods employed must accomplish these things They must temporarily stop all activity so that the normal pacemaker can again dominate heart activity they must leave excitability and those processes which originate excitation in the pacemaker relatively unimpaired and they must so act that conduction of the impulse can again occur at an approximately normal velocity and follow pathways which will initiate a normal sequence of events One difficulty encountered in employing drugs and other means of defibrillating the heart is due to the fact that duality of actions occur Local applications of cold or potassium chloride may initiate fibrillation while general application may abolish it In certain doses some drugs have a favorable effect but in other concentrations they actually promote the condition which it is desirable to terminate and prevent.

Fibrillation of the auricle and ventricle can be produced or stopped by use of potassium chloride solutions (Hering 1907 Erlanger, 1912 Garrey, 1924 Hooker 1929, Wiggers et al, 1930) Excess potassium ion reduces membrane potential and the excitability of a tissue (Chapter 10) Potassium chloride injected into the circulation and brought to cardiac muscle by the blood flow which is maintained by cardiac massage will stop fibrillation due to a reduction of excitability and a block of conduction If excitability can then be restored by washing out the potassium or counteracting it by injections of calcium a normal rhythm may be

two to three amperes at 160-180 volts was employed in most instances. In each case, successful defibrillation was accomplished within 30-45 seconds of its onset by means of one or very rarely two countershocks Because the period of interrupted circulation was brief, no cardiac massage was required (see Wiggers 1953)

Some additional comment on the magnitude of the defibrillating current requirement is advisable. It appears that defibrillation can be accomplished only if uniformity of state can be restored to all myocardial units. This circumstance may be one of complete polarization or complete depolarization and may result from countershock, cold, KCl, or other agents. When electrical countershock is employed as the defibrillating stimulus it influences various parts of the myocardium in proportion to the current density present across the membrane of the component cells Regardless of the total current passed, if any area of ventricular muscle is not depolarized by the defibrillating shock, asynchrony of activity will persist and fibrillation will continue when the countershock ends. Furthermore in the presence of high resistance areas contiguous to the myocardium (such as pericardial or subepicardial fat) the major voltage drop will occur

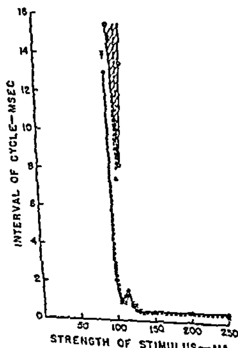


FIGURE 60 Strength interval curve and vulnerable period (▨) of the dog ventricle before fibrillation (•—•) and after defibrillation by a counter shock (x——x) (Hoffman et al., Circulation Research 1950)

measure in certain circumstances is not an uncommon clinical procedure (Beck et al, 1947, Beck and Rand, 1949, Southworth et al, 1950)

1 *Techniques of defibrillation* Methods of defibrillating the heart with and without opening the chest have been sought for some time (Ferris et al, 1936, Guyton and Satterfield, 1951, MacKay et al, 1953, Leeds et al, 1951, Lape and Mason, 1953) The difficulty involved in the closed chest preparation is that of obtaining a current flow of sufficient density in all parts of the heart To accomplish defibrillation either all fibers must be excited at once or the ones which can be excited held in a depolarized state until the remaining elements can be brought into a uniform condition This must be accomplished without injury to the central nervous system or other structures of the body A difficulty encountered in defibrillation with the chest closed is that cardiac massage cannot be employed and the countershocks must be applied before the heart and central nervous system have suffered irreversible damage from anoxia due to failure of the pumping action of the heart Suitable instruments and techniques, although they have been used with success to defibrillate the hearts of dogs and other large animals without opening the chest, are never as reliable as are the methods for defibrillating the exposed heart

Most of the methods mentioned have been tried at one time or another in various studies in this laboratory, the use of alternating current in the fashion discussed below, has been found most effective in all cases of fibrillation in open chested dogs (Hoffman, et al, 1955) In this work, the onset of fibrillation was recognized immediately from the typical electrocardiographic pattern on a monitoring oscilloscope As soon as such a tracing appeared, all electrode connections to the dog were open circuited to prevent a heavy current from flowing through any such electrode during the actual defibrillation Such current flow if permitted, was found to cause tissue damage or actual burning Subsequently, the approximated margins of the sternum were parted and two large, moist, padded electrodes were applied to opposite sides of the ventricle These electrodes were spoon shaped and well insulated on all surfaces except that actually making contact with the myocardium As soon as the electrodes were in position, a burst of 60 cycle current was supplied from a defibrillator with an "on" cycle of 0 4-0 6 seconds During the "off" cycle the electrogram was observed on the oscilloscope and defibrillation, if accomplished, could be recognized If the electrogram revealed a persistence of the arrhythmia, a second countershock was given A current of

across these rather than across the cardiac cells For these reasons it seems advisable to employ, at all times, a defibrillating current that is a multiple of the minimal effective value Such may be insured by eliciting an adequate voltage from the defibrillator

2. *Effects of defibrillation* This technique was evaluated in the following manner Tests of excitability and vulnerability were resumed immediately after the defibrillation had been accomplished and were repeated at brief intervals for periods ranging up to several hours In over 50 per cent of the tests the procedure described above produced *no* significant change in either the strength interval curve or the magnitude and position of the vulnerable period (Figure 60) (Hoffman et al, 1955) Such changes as were encountered in other experiments were often no greater than the spontaneous variations reported in Chapter VI Furthermore in many instances even repeated fibrillation and defibrillation failed to alter the minimum diastolic thresholds minimum fibrillation thresholds the duration of the absolute total and relative refractory periods, or the mean blood pressure by more than the normal variation between tests (Table 6)

In some experiments however large changes were observed in the various parameters of excitability Both increases and decreases in thresholds occurred and such changes were long lasting or permanent. The fact that often such threshold changes were *not* associated with any alteration in refractoriness or vice versa, suggests that displacement of the test electrodes rather than a true change in excitability explains many of these instances since each counter-shock produced a generalized convulsive movement of the entire dog During this convulsive movement, the defibrillating electrodes often struck the small test electrodes sewn to the ventricular epicardium.

In the experiments designed to test the action of fibrillatory and antifibrillatory drugs the results reported are based only on those cases wherein the limits of the vulnerable period could be accurately and consistently outlined during control periods and where defibrillation was not accompanied by any appreciable change in excitability of the ventricular myocardium.

3 *Mode of action of electric countershock* Figure 61 A attempts to portray in a simplified manner the excitability conditions in ten adjacent myocardial units of a fibrillating ventricle The duration of absolute and relative refractoriness has been arbitrarily represented Figure 61 B is an attempt to represent diagrammatically the defibrillating effect of a 60 cycle alternating current of adequate voltage acting during 0 1 sec on

TABLE 6.—*The Effect of Repeated Defibrillation on Excitability*

Exp	Test	Mean B P	Diast Threshold		Low Fib Threshold		Tot Ref Period		Abs Ref Period		Test Duration msec	Cycle Length msec
			Control	Post Fib	Control	Post Fib	Control	Post Fib	Control	Post Fib		
5/15/53	Control	100	0.24		8.5		150		100		5 0	250
	P F 1	100		0.28		9 5		130		90	5 0	250
	P F 2	110		0.28		8 7		130		90	5 0	250
	P F 3	90		0.27		9 5		130		90	5 0	250
	P F 4	110		0.27		9 0		130		90	5 0	250
6/21/53	Control	90	0 15		3 0		150		95		12.0	250
	P F 1	90		0 18		3.2		150		95	12 0	250
6/17/53	Control	90	0.5		10 0		185		135		3 0	300
	P F 1	90		0.5		10 0		185		130	3 0	300
1/21/53	Control	115	0 37		13 0		170		95		10 0	300
	P F 1	85		0.36		13 0		170		90	10 0	250
12/22/53	Control	85	0 44		12.5		140		105		3 0	250
	P F 1	70		0'49		13.5		135		105	3 0	250
10/13/53	Control	80	0.55		14.5		142		110		3 0	250
	P F 1	90		0.55		14 0		140		105	3 0	250
7/10/53	Control	90	0.39		8.5		170		130		2 0	300
	P F 1	75		0 50		8 0		160		130	2 0	250
	P F 3	70		0.54		8 5		160		130	2 0	250
7/17/53	Control	85	0.50		8.2		125		90		3 0	250
	P F 1	85		0 41		7.5		130		90	3 0	250
	P F 3	90		0 60		12 5		130		90	3 0	250
	P F 5	80		0 75		11 5		145		95	3 0	250

the same fibers shown in Figure 61 A It shows that such a stimulus brings all elements to a uniform state and after the current ceases permits a synchronous response to the normal pacemaker A coordinated beat will then be the result and a normal rhythm will ensue (Orias, 1953)

THE PREVENTION OF FIBRILLATION—THE ACTION OF ANTIFIBRILLATORY DRUGS

The literature dealing with the antifibrillatory drugs is tremendous and numerous attempts have been made to review recent important contributions (Dawes 1946-1952, DiPalma and Schultz 1950 Van Dongen and Taal 1950 Sokolow 1951) In this laboratory the actions of several antifibrillatory agents have been studied during a period of several years In some cases the object of the investigation was to evaluate the therapeutic effectiveness of a particular compound or series of compounds, in most instances however the main interest was directed toward determination of the relationship between antifibrillatory action and the particular changes in cardiac excitability which might explain this action. In the present discussion, this latter emphasis will be maintained the original publications (Gilbert, et al 1951 Woske et al., 1953, Mirkin et al., 1954 Belford et al. 1956) can be consulted for detailed studies of any particular drug

QUINIDINE Quinidine sulfate was administered by means of two different techniques In one series of experiments the compound was injected by means of a constant intravenous drip at rates ranging from 5-30 mg/kg/hr with a total dose of 5 25 mg/kg In a second series a similar dose range was employed but the injections were delivered from a constant speed syringe within a period of 10-20 minutes Results from both series were comparable and will be discussed together In all cases the injection rate was slow enough to prevent any marked prolongation of intraventricular conduction time. Similarly hypotension (mean blood pressure below 60 mm. Hg) was avoided in most instances and all experiments reported are those in which mean blood pressure remained above this level for the duration of the test period

In a number of experiments, repeated determinations of the concentration of quinidine in the blood were made simultaneously with each test of excitability or vulnerability Finally in most cases tests of excitability were continued until the blood levels of the administered quinidine had diminished so that any changes in excitability recorded during and follow

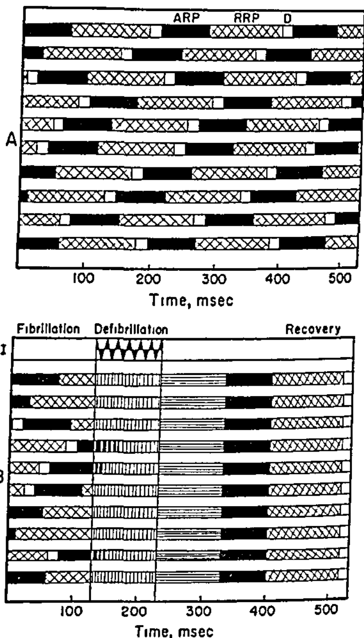


FIGURE 61 *A* Diagram of behavior of individual myocardial fibers during fibrillation showing a short diastole (D) the absolute (ARP) and relative (RRP) refractory periods

B Termination of incoordinated activity by a defibrillating countershock and restoration of normal rhythmic activity (Orias Acta physiol. Lat Amer., 1953)

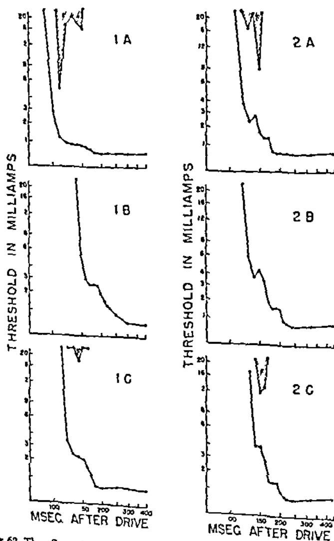


FIGURE 62. The effect of quinidine (3-6 mg./L.) on the vulnerability of the dog heart (cross-hatched area). Auricle (1) ventricle (2) A—control B—maximum effect C—early recovery

ing drug administration could be evaluated with respect to both pre- and post treatment control values (see also Wegria and Boyle, 1948)

1 *Effects on auricular excitability and fibrillation thresholds* The changes in auricular excitability resulting from administration of quinidine sulfate were qualitatively similar to results reported by others (Moisset de Espanes, 1937, Wedd et al, 1942, Goodman and Gilman, 1955) The magnitude of these changes, however, was definitely less than would be expected from the classical studies of Lewis (1921, 1926) on the dog ventricle In representative experiments the total refractory period was prolonged by approximately 50 msec, the absolute refractory period by 20 msec, and thus the duration of the relative refractory period by 30 msec The recovery of excitability during the relative refractory period was slowed, as well as prolonged, so that thresholds during this interval of the cardiac cycle were considerably elevated above control values (Figure 62 and 63) The dip in the strength interval curve, when revealed by control observations, was not abolished by quinidine and maintained the same relative position in the relative refractory period Minimum thresholds during the dip, however, were elevated in proportion to the alteration produced in the remainder of the curve (Figure 62 and 63)

The level of resting excitability, as indicated by thresholds for extra systoles during diastole, was definitely changed by quinidine Diastolic thresholds were consistently elevated, by as much as 40% above the control values This, and the increase in total refractoriness, were the most prominent changes encountered Intra auricular conduction velocity was slowed by the doses of quinidine employed, interelectrode conduction times were increased by about 10% in most cases, although such changes were more prominent immediately after drug administration(see also Brown, 1952)

Concomitant with the above changes in excitability there was an abolition of fibrillation resulting from suprathreshold test pulses applied at any interval of the cycle (Figure 63) The minimum blood concentration of quinidine producing abolition of fibrillation was found to be approximately 3 6 mg/l, a similar blood level was necessary for the changes in excitability mentioned above

Although there was often a temporal coincidence between the prolongation of the total refractory period and the abolition of fibrillation, in other experiments this relationship failed to maintain At times the boundary of the total refractory period was extended without any significant

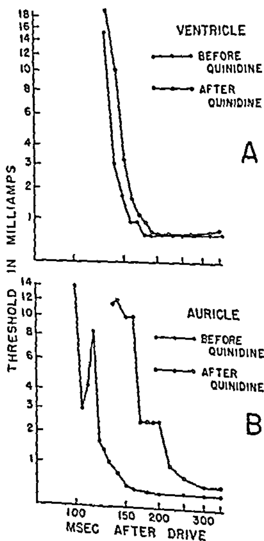


FIGURE 63 The effect of quinidine (3-6 mg./L) on the recovery of excitability in the ventricle (A) and auricle (B) of the dog heart.

TABLE 7.—*Action of Quinidine on the Dog Heart*

A Auricle

Exp N	Increase in ARP msec	Increase in TRP msec	Increase in QT	Increase Latency	Anti fib	Dose mg/kg/min		Maximum Blood Level	Change in Dist. Thres. & Thres. in ma.
165	15	85			+	8	15	3.2	−.03 (.50)
180	20	30	25	9	++	10	20	6.0	+.04 (.56)
183	5	40	25	10-15	0	10	20	3.0	+.25 (.725)
185	10	10	20	23	++	10	18	3.2	+.22 (.40)
188	20	75		10-20	++	10	20	2.2	+.16 (.38)

B Ventricle

Exp N	Increase in ARP msec	Increase in TRP msec	Increase in QT	Increase Latency	Anti fib	Dose mg/kg/min		Maximum Blood Level	Change in Dist. Thres. & Thres. in ma.
180	5	10	25	+12		10	20	6.0	+.08 (.56)
183	5	5	25	Equivocal		10	20	3.0	+.10 (.45)
185	0	10-15	20	No Change		10	18	3.2	−.07 (.72)
188	25	25	Not Measurable	—		10	20	2.2	−.04 (.55)
A 1	0	10	0	−5	+	10	20	3.0	+.05 (.55)

0 = No effect on fibrillation + = Vulnerability reduced ++ = Fibrillation Prevented

B Changes in Ventricular Diastolic Thresholds with Administration of Quinidine

Exp No	D of Stim., msec.	Dose, mg/kg	Control thresh., ma.	Max. thresh., ma.	Recov thresh ma.	Max. chg %	Recov thresh., %
65	1	9	1 7	3 4	3 4	100	100
72	1	15	1.8	3.5	3.2	94	78
77	1	10	1.2	1 45	1.2	21	0
80	1	7 4	1 9	4 0	1.8	110	−5.2
83	1	12.6	1.55	4 75	1.8	206	16.6
87	1	7	1 70	3 0	2.25	77	47
93	1	15	1.32	3 1	2.7	135	104
94	1	5	1 15	1 48	.98	29	−14
95	1	25	2.1	3.8	2.9	81	38
Average		11.8	1.60	3 17	2.25	95	40.5
65	13	9	12	.27	.20	125	67
72	13	15	10	18	14	80	40
77	13	10	.05	08	.07	60	40
80	13	7 4	10	15	10	50	0
83	13	12.6	.075	15	075	100	0
87	13	7	06	11	10	83	67
93	3	15	12	.25	16	108	33
94	3	5	11	19	.07	73	−36
95	3	25	.22	.37	.27	68	23
		11.8	106	195	132	83	26

in the auricle thresholds during the relative refractory period were considerably elevated the entire strength interval curve being shifted up and to the right the dips although revealed by stimuli of greater intensity than during control conditions maintained their usual positions in the relative refractory period.

Changes in the level of resting excitability were more prominent in the case of the ventricle than in the case of the auricle As shown by Table 8-B the average increase in diastolic thresholds for stimuli of a wide range of durations varied from 80-110% This increase is of real significance since in most experiments diastolic thresholds returned toward control values after an adequate lapse of time. The doses of quinidine employed produced only transient changes in intraventricular conduction time As in the case of the auricle the minimum blood level of quinidine resulting in the changes discussed above was between 3 6 mg/l. Similarly it was not possible to relate an alteration in any one specific parameter of excitability to the abolition of fibrillation in all instances the most

change in vulnerability, in other cases, fibrillation could not be produced at times when the total refractoriness was little changed from control values Similarly, a lack of correspondence was observed between changes in the absolute refractory period and vulnerability (Table 7) The significance of these findings will be discussed below, in a section devoted to the relationship between changes in excitability and antifibrillatory actions of all drugs studied

2 *Effect on the ventricle* The effect of quinidine on the excitability of ventricular muscle was quite similar to that described for the auricle In terms of the relative magnitude of the changes in refractoriness, however, there were significant differences in most instances In representative experiments the total, relative, and absolute refractory periods were prolonged by 50, 30, 20 msec (Figure 62 and 63 respectively) This change was not encountered in all cases, however, as can be seen in Table 8 A As

TABLE 8

A Changes in the Absolute Refractory Period (A R P) of the Ventricle and Administration of Quinidine

Exp No	Dur of Stim msec	Control ARP msec	Max ARP msec	Recov ARP msec	Max Change %	Recov %
65	1	130	180	140	38 4	7 7
72	1	180	190	160	5 5	−11 0
77	1	130	150	150	15 3	15 3
80	1	160	190	190	19	19
83	1	180	190	170	5 5	−5 5
87	1	150	170	140	13 3	−6 8
93	1	145	170	150	17.2	3 4
94	1	190	235	215	23 6	13
95	1	135	145	115	7 4	−15
Average		155	180	159	16 1	2.2
65	13	90	100	90	11	0
72	13	110	140	110	27	0
77	13	80	90	90	12 5	12.5
80	13	115	135	130	17 3	13
83	13	130	130	120	0	−7 7
87	13	85	105	80	23 5	−5 9
93	3	120	135	95	12 5	−21
94	3	155	190	155	23	0
95	3	120	120	105	—	−12.5
Average		112	127	108	14 1	−2 4

It was noted in a number of experiments (excluded from general consideration) that when the mean blood pressure fell below 60-65 mm.Hg the administration of the usual doses of quinidine failed to produce the usual changes in either excitability or vulnerability A similar observation has been reported by others (Wegria and Nickerson, 1942 Wegria and Boyle, 1948)

PROCAINE AMIDE It has long been known that cocaine and procaine have an antifibrillatory action Cocaine (Herman and Jordan, 1931) has some protective action against fibrillation of the heart by direct stimulation or epinephrine-chloroform action Procaine not only protects against fibrillation by anesthetic agents (Shen and Simon 1938 Burstein and Marangani 1940, Long et al 1949) but also tends to prevent production of auricular flutter and fibrillation by other means (Hirschfelder and Tamacales 1942 Brown and Acheson 1951) This drug has an antifibrillatory action on the ventricle (Van Dongen 1936 1938 Wiggers and Wegria 1940, Wiggers and Pinero 1940, Dawes 1946) More recently procaine amide (the diethylaminoethyl amide of p aminobenzoic acid) has come into general use (Wedd et al, 1951 Miller et al., 1952, Zapata Diaz, 1952) There is strong similarity between its action and that of quinidine. It is less potent in many actions than procaine or quinidine but appears to have some compensatory advantages (Newman and Clark, 1950 Goodman and Gilman 1955)

In studies of the action of procaine amide (Woske et al. 1953) on excitability and vulnerability to fibrillation of the auricle and ventricle techniques similar to those employed in testing the action of quinidine were used The dose employed, 30-40 mg/kg was administered intravenously at a constant rate during a ten minute interval. Blood levels were determined by the method of Mark et al., (1951)

1 *Auricular excitability and fibrillation* The total refractory period was increased much more than the absolute thus the processes of the relative refractory phase were most affected (Figure 64-C) The time course of return of excitability to the diastolic level was somewhat prolonged by this agent but the configuration of the strength interval curve was essentially the same before and after drug administration The major dip in the excitability recovery curve was not consistently altered by full doses of procaine amide.

Changes in the level of resting excitability were somewhat complex. Although there was little alteration in diastolic thresholds to test shocks

frequent association, however, was between the elevation in diastolic threshold and a decrease in vulnerability Unlike the auricle, however, fibrillation often was not abolished by the doses of quinidine employed, although its production by a single test pulse was made more difficult in terms of current requirement

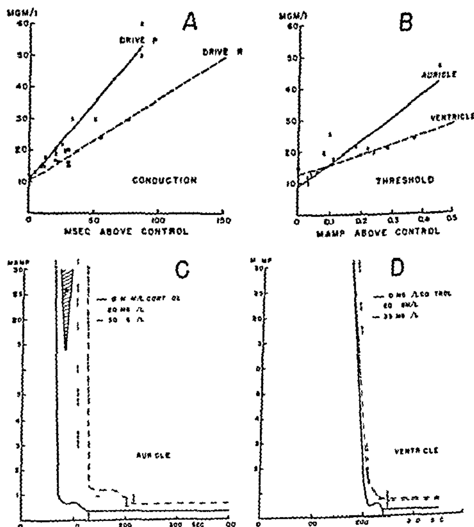


FIGURE 64 The effect of procaine amide on conduction (A) in auricle (Drive P) and ventricle (Drive R) as related to blood level of drug on auricular and ventricular diastolic thresholds (B) on auricular (C) and ventricular (D) *refractoriness Note* abolition of vulnerability (cross hatched area) in C during drug action (Woske *et al* J Pharm & Exper Therap 1953)

little tendency for the refractory periods to return to control values even though the blood level fell quite markedly

The threshold of resting excitability in the ventricle was changed even more markedly than that of the auricle by similar concentrations of the procaine amide Thus thresholds to test shocks of 0 1 m ec. duration were increased by 60-70% in representative experiments This change in excitability was related to the blood level of the drug (Figure 64-B) immediately after injection but after an interval of time excitability began to return to or toward normal at a much faster rate than the blood level Interelectrode conduction times in the ventricle were increased slightly by the usual levels of procaine amide (see Figure 64-A) but the most marked change occurred in A V conductivity *Auriculo-ventricular* conduction time was often increased by as much as 100 msec., and with higher blood levels transient partial or complete A V dissociation was produced.

The doses of procaine amide employed were adequate to completely prevent the initiation of fibrillation in some cases and to produce a marked elevation in thresholds for multiple extrasystoles or fibrillation in others This striking change in vulnerability in the absence of any appreciable alteration in the duration of refractoriness will be discussed more fully in a subsequent section

ISOQUINOLINE COMPOUNDS Numerous other compounds having structural relationship to quinidine and procaine have a similar antifibrillatory action (Dawes 1946 1952 Burno 1954) Several new antifibrillatory agents were tested in a limited series of experiments Two of these SKF #531 [1—(2-diethylaminoethylamine) 3—methylisoquinoline dihydrochloride] and SKF #532 [1—(2-diethylaminoethylamino)—3 propylisoquinoline] were studied and present interesting comparisons with quinidine and procaine amide. The results of these experiments will be summarized briefly below

1 *Action of SKF #531* This agent was employed in doses of 1.25-5 0 mg/kg and administered by slow intravenous injection Blood levels were not determined The effects at the higher dose levels were as follows. In both the auricle and ventricle, diastolic thresholds to test pulses of a wide range of durations were *increased* by as much as 100-200% above control values The duration of the absolute and relative refractory periods was increased from 15-40% in representative experiments the duration of the total refractory period was thus prolonged quite markedly

of long duration, when a *short* test pulse (0 1 msec) was employed diastolic thresholds were elevated by approximately 50% during the period of initial high blood levels of procaine amide Furthermore the magnitude of the increase in threshold was related to the blood level of this agent (Figure 64-B) However, even though the blood concentration of procaine amide remained elevated, the thresholds for short pulses during diastole always returned toward control values It appears that factors other than the concentration of the drug in blood and tissues at any one time should be considered in estimating its effect upon cardiac responses

It was found that a blood level of approximately 20 mg/l was necessary to produce a significant alteration in diastolic excitability Above a blood level of 20 24 mg/l there was a significant prolongation of intra auricular conduction time the increase ranging from 10 60 msec and usually amounting to 20 30 msec (conduction was measured between the right and left auricular appendages) This change was also related to the blood level of procaine amide, as seen in Figure 64 A Blood pressure changes did occur when this agent was injected, but the technique employed in the experiments reported here resulted in a transient drop of only 10 20 mm Hg mean pressure

Auricular fibrillation could no longer be induced by single test shocks after the administration of this agent in the amounts employed Furthermore in several instances a long lasting spontaneous fibrillation was promptly abolished by injection of procaine amide This change in vulnerability is demonstrated in Figure 64-C The relationship between excitability changes and vulnerability will be discussed below, along with results obtained from the ventricle

2 *Ventricular excitability and vulnerability* The refractory periods of the ventricular myocardium were little influenced by the same concentrations of procaine amide found quite effective in the case of the auricle (Figure 64-D) The absolute refractory period was increased by less than 20 msec in representative experiments, a change only slightly greater than that which might result from spontaneous variation Similarly, the duration of total refractoriness was never increased by more than 30 msec Despite the fact that the boundaries of the refractory periods could be accurately determined, it was impossible to relate changes therein to the blood level of procaine amide with the exception that no alteration in refractoriness resulted from procaine amide blood levels below 20 mg/l During a period of one to two hours after a single injection there was

These results are seen in Figure 65 A and B Interelectrode conduction time in both chambers was increased by this dose level though not to a great extent. Occasionally ventricular arrhythmias were encountered immediately after the termination of the injection

In both the auricle and ventricle SKF #531 provided significant protection against fibrilation in that thresholds for multiple extrasystoles were r ... test shocks at the highest intensi ... As sh ... in the ... maxim ... thresh

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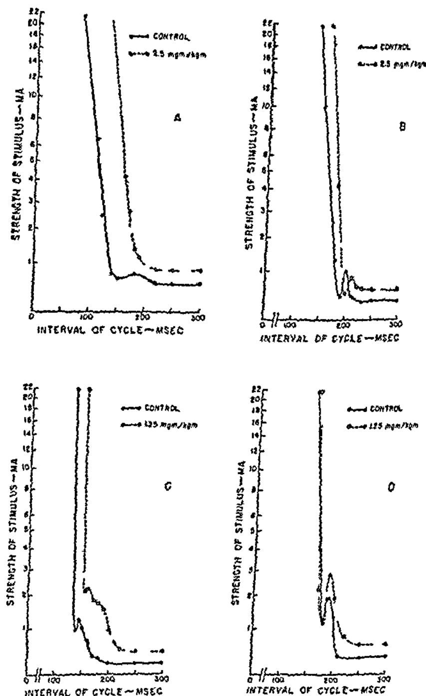


FIGURE 65 Effects of isoquinolines on recovery of excitability in auricle (A C) and ventricle (B, D) Top, SKF #531A bottom, #532A

These results are seen in Figure 65 A and B Interelectrode conduction time in both chambers was increased by this dose level, though not to a great extent. Occasionally ventricular arrhythmias were encountered immediately after the termination of the injection

In both the auricle and ventricle SKF #531 provided significant protection against fibrillation in that thresholds for multiple extrasystoles were markedly increased and often only long test shocks at the highest intensity delivered by the stimulator (30-40 ms) could elicit this response. As shown by Table 9 results were uniformly better in the auricle than in the ventricle but in neither case was it possible to relate the period of maximum protection against fibrillation to either the elevation of diastolic thresholds or to the prolongation of the refractory periods in all animals.

2 *Action of SKF #532* This latter compound was employed in similar doses and injected at the same rate as SKF #531 Although the changes in excitability resulting from this agent were of the same type as described above for the methylisoquinoline, the magnitude of change in refractoriness and diastolic excitability was much less (Figure 65 C and D) Protection against auricular fibrillation was obtained at a dose level of 2.5 mg/kg and successive doses were increasingly effective demonstrating some cumulative action. The antifibrillatory potency of this agent for the ventricle was less than for the auricle and again it was not possible to relate degree of protection against the induction of fibrillation to the magnitude of change in refractoriness or diastolic excitability in all cases

SUMMARY In conclusion it can be stated that all the antifibrillatory drugs tested did reduce vulnerability to the production of fibrillation by electrical stimulation. These drugs caused definite prolongation of the irresponsive or refractory period and an even greater percentage rise in thresholds A slowing of conduction also occurred The slowing of the recovery following activity and the decrease in excitability showed no quantitative correlation with the change in fibrillation threshold It seems reasonable to assume therefore, that the actions of antifibrillatory agents involve more than a mere change in excitability and the length of the refractory period A discussion of the action of antifibrillatory drugs will be given later in this chapter

It should be stated that a number of special control experiments were done in connection with this study of fibrillatory and antifibrillatory drugs In one set of experiments the effects of blood pressure changes were studied because quinidine and some of the other antifibrillatory agents

TABLE 9—*The Effects of Certain Isoquinoline Compounds on the Dog Heart*

Dose mg/kg	Diastolic Thresholds	Refractory Period		Conduction Time			Comment
		Absolute	Total	Aur	A V	QRS	
531 A, Auricle—Maximum Effect*							
5 0	36	120	75	280	50	33	Fibrillation abolished Multiples present
2 5	106	43	27	40	11	0	100% Protection Fibrillation abolished
2.5	17	63	33	22	19	—35	Occasional multiples
531 A Auricle—Maximum Protection*							
5 0	8	100	100	280	50	33	Fibrillation abolished
2 5	106	43	27	40	11	0	Fibrillation abolished
2.5	17	63	33	22	19	—35	Fibrillation abolished
531 A and 532 A Ventricle—Maximum Effect*							
2 5	178	15	11	0	0	0	Multiples abolished†
2 5	255	—7	—13	50	33	150	Fibrillation abolished†
2 5	0	8	10	40	11	0	Fibrillation abolished
5 0	123	4	7	—	—	—	No protection

*Values expressed as percentage changes from control values
†532 A

often affect blood pressure It has been reported that quinidine fails to act as an antifibrillatory agent if blood pressure is too low (Wegria and Nickerson, 1942) In this series of experiments low blood pressure levels were produced by hemorrhage and high levels by transfusions and clamping of the abdominal aorta The effects of periods of acute hypotension and hypertension on cardiac excitability, conduction, and vulnerability to

fibrillation were neither very great nor of a constant nature in either the normal or denervated heart. Cutting the sympathetic fibers to the heart did cause a slight transient lowering of excitability The conclusion drawn was that blood pressure changes in themselves did not determine the actions of drugs nor did they have a definitely calculable effect on those aspects of heart action under investigation These conclusions however, should not be taken to indicate that long lasting blood pressure changes resulting in an impaired blood supply, anoxia, blood carbon dioxide and pH changes would not affect cardiac excitability and vulnerability to fibrillation

A second series of control studies was carried out because most experiments were performed on animals anesthetized with membutal In this series dogs were decerebrated under ether or a very short acting barbiturate. Tests of conduction excitability and fibrillation thresholds were made and then pentobarbital was given in quantity sufficient to produce a degree of anesthesia normally attained A transient rise in thresholds a prolongation of the refractory period and a decrease in vulnerability were found immediately after an intravenous injection of this drug but the effects soon became minimal Intraperitoneally injected doses had no specific depressant action on the heart until dose levels were much higher than the range generally employed

It was felt that the antifibrillatory actions observed in this study of drugs were not secondary to their transient effects on blood pressure nor modified by the effects of the anesthetic employed

AGENTS ENHANCING VULNERABILITY TO FIBRILLATION

Before entering into a discussion of the possible mode of action of the antifibrillatory drugs it is of interest to compare their effects on the various parameters of excitability and response with changes resulting from agents known to enhance the vulnerability of the myocardium to the same arrhythmias The fibrillation producing tendencies of a number of quite different drugs have been investigated and the major emphasis placed on sympathomimetic and parasympathomimetic compounds In addition reference will be made to minor studies in illustrating certain points The conclusions drawn are based principally on a consideration of the actions of drugs most thoroughly studied in this laboratory

The first statement that can be made is that the cardiac effects of drugs which have been shown to produce fibrillation under specific condi

tions are so diverse that it is *probable that several different mechanisms* are involved and fibrillation may result from a variety of drug actions Drugs which are good antifibrillatory agents under normal conditions actually produce fibrillation in other circumstances For example, procaine amide is reported to induce ventricular fibrillation in all hypothermic dogs *(Covino et al, 1955) Fibrillation is merely a disorganized activity of the* fibers of the myocardium and this might be produced in several different fashions

THE EFFECTS OF HYDROCARBONS, AMARIN AND VERATRUM ALKALOIDS It is well recognized that certain of the volatile anesthetics, a number of other hydrocarbons and volatile halides and quite a few other drugs are likely to cause fibrillation or more particularly *to so* affect the heart that sympathetic nerve stimulation or epinephrine administration will cause a precipitous initiation of ventricular fibrillation (Dawes, 1952, *Goodman and Gilman,* 1955) The drugs of this *category* which *have been studied* to some extent in this *laboratory* are *chloroform,* benzene, amarin and veratrum alkaloids

1 *Chloroform* Levy (1911, 1913, 1914) found that ventricular fibrillation could be induced in animals under light chloroform anesthesia by injections of epinephrine but under deep anesthesia this sensitivity is lost. Reflex or direct excitation of cardiac sympathetic *fibers has the* same fibrillation producing effect in lightly anesthetized animals It was found *that cyclopropane has a similar action to that of chloroform* and that numerous other sympathomimetic amines and related drugs will act to initiate fibrillation in association with these anesthetics (Orth et al, 1938, Meek, 1940, 1941 Rennick et al, 1951, Deterling et al, 1954)

Sasaki (1921) and Acierno and DiPalma (1951) have obtained evidence *that chloroform depresses excitability but shortens the refractory* period It has been found with the techniques employed in this laboratory that chloroform in small doses does often shorten the refractory period and may increase excitability slightly Greater concentrations have a definite depressant action raising threshold to stimulation and prolonging *the refractory period beyond the control duration* The vulnerability to fibrillation elicited by test shocks is not significantly altered in the denervated heart by this agent *It is* concluded that the combined depressant and excitant action initiated by the drug in situations during which the vagi and the sympathetic nerves are also brought into action is really *responsible for the occasional occurrence of fibrillation* during chloroform

anesthesia (Salter 1952 Riker et al., 1955) This conclusion is supported by the following evidence.

The rise in arterial pressure on epinephrine injection seems to contribute to the development of fibrillation (Murphy et al, 1949) The reflex activation of the vagus which depresses pacemaker tissue (Hoff and Nahum 1934) at a time when epinephrine tends to increase automaticity would favor development of ectopic beats It is also recognized that vagus stimulation and acetylcholine can promote fibrillation (see later) Atropine tends to prevent development of arrhythmias under these anesthetics (Seevers et al. 1934) Parasympathetic sympathetic and ganglionic blocking agents also tend to prevent fibrillation (Meek, 1940, 1941 Troch, 1953 Glassman et al., 1953) Depressants acting on the heart also increase susceptibility to fibrillation until they have caused a deep depression and this likewise suggests that a hyperexcitability coupled with some selective depression may be contributory (Levy, 1920 White et al. 1955)

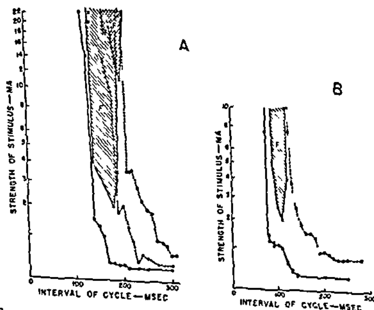


Figure 66. The effect of amarin on excitability and vulnerability (II I III) A—Auricle Control (•—•) 5 mg/kg (•———•) 10 mg/kg (o———o) B—Ventricle Control (•—•) and 10 mg/kg (o———o) Note that ventricular vulnerability was completely abolished.

TABLE 10—*The Effect of Amarin on Properties of the Heart Muscle in a Sample Experiment*

		Control value in msec	Amarin 5 mg/kg msec	Amarin 10 mg/kg msec
Auricle	Absolute Refractory Period	127	168	183
	Relative Refractory Period	46	72	88
	Total Refractory Period	173	240	271
	Interelectrode conduction time	40	50	65
Ventricle	P R Interval	75	90	120
	Absolute Refractory Period	161	181	190
	Relative Refractory Period	50	78	110
	Total Refractory Period	211	259	300
	Interelectrode conduction time	40	50	50

2 *Benzene* This drug, like chloroform, in weak concentrations has little effect on diastolic threshold and does not markedly lower thresholds to fibrillation It may shorten the refractory periods of the auricle but in higher concentrations definitely lengthens the duration of refractoriness The fibrillation which results from the combined action of this drug and epinephrine is also presumably due to a mixture of excitatory and depressant effects on the heart

3 *Amarin hydrochloride* The cyclic amidine derivative 2, 4 5 triphenyl dihydro iminazole is known to cause profound bradycardia and a slowing of conduction in the heart When epinephrine is administered following amarin the combined action of these drugs causes fibrillation (Fastier and Smirk, 1948) A series of experiments was performed in which a determination was made of the effect of this drug on excitability, the duration of refractory periods and the vulnerability of the dog auricle and ventricle to fibrillation by single electrical stimuli It was found that doses of 5 to 10 mg/kg of body weight raises the auricular diastolic threshold by 30 to 50 per cent (from 0 48 to 0 71 ma on the average) and the ventricular threshold even more markedly (from 0 28 to 0 46 ma) Both the absolute and relative refractory periods are prolonged (Figure 66) and conduction is slowed in auricle, ventricle and specialized conducting tissues (Table 10) Fibrillation thresholds are actually raised by the smaller doses of amarin and in some instances fibrillation could no longer be produced by single electric shocks of 20 to 30 ma even when applied during what had previously been shown to be the vulnerable period Doses of drug higher than 15 mg/kg did frequently produce a slow

disorganized beat of the ventricle and epinephrine did cause fibrillation and a failure of cardiac pumping action

The depressant action of amarin does initially decrea e the vulner ability of the heart to fibrillation by electrical stimuli Excessive depression, however eventually results in disorganization of the heart. A mixture of depressant and excitant actions creates a situation to which the heart is most vulnerable and the action of amarin coupled with that of epinephrine causes immediate fibrillation Attempts to drive the heart faster than usual after amarin has slowed conduction likewise produced fibrilla tion This study of amarin gives good evidence in support of the hypothesis that fibrillation can result from a multiplicity of causes enhanced excit ability excessive depression but most readily from a mixture of excitatory and depressant influences (see Fa.tier, 1951)

4 *The veratrum alkaloids* It is known that in large doses veratrum alkaloids cause cardiac arrhythmias and eventually induce ventricular tachycardia and fibrillation (Krayer and Acheson 1946 Goodman and Gilman 1955 Kosterlitz et al., 1955) In experiments designed for the study of excitability conduction, the duration of refractoriness and vul nerability to fibrillation it was found (Matsuda et al, 1953) that a crude

TABLE II—*The Action of Veratrum Alkaloids on the Auricle and Ventricle of the Dog Heart*

Dose of Drug mg/kg	Absolute Refractory period	Relative Refractory period	Total Refractory period	Diastolic Threshold	P R Interval	Inter Electrode Conduction Time msec
Auricle						
Cryptenamine						
Exp. #5 Control	95	45	140	0.35	90	30
0.3	105	50	155	0.35	105	30
0.5	120	60	180	0.40	122	44
0.9	135	65	200	0.42	135	52
1.3	145	60	205	0.43	145	65
Ventricle Veratrine					Q T Interval	
Exp #7 Control	1[illegible]0	55	205	0.30	200	5
0.1	150	65	215	0.32	210	5
0.3	170	55	225	0.40	225	7
0.5	180	75	255	0.65	250	11
1.0	165	45	210	0.68	270	13

FIGURE 67 A. The action of veratrine as indicated by the transmembrane action potentials of a ventricular fiber The sequence of pictures *from top to bottom* and *left to right* shows the progressive effect of the drug Each picture (except the bottom) gives a single spontaneous action potential. The bottom picture shows a series of partial depolarizations typical of the arrhythmia created by the drug (Retouched to show *action potential upstrokes by dotted lines*)

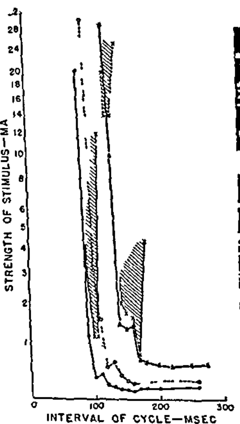
B The effect of veratrine on the recovery of excitability in the dog ventricle

preparation of veratrum alkaloids (S B Penick & Co) cryptenamine and also cevadine produce a moderate prolongation of the total refractory period of the auricle and ventricle of the dog heart. Both the absolute and relative refractory periods are prolonged excitability is decreased and conduction, particularly in the A V bundle is markedly slowed (Table 11 Figure 67)

Small doses of the veratum alkaloids used either did not change the threshold of auricular and ventricular vulnerability or definitely raised the threshold a decreased threshold was not encountered (see also Wedd and Drury, 1926) In one out of 12 experiments employing such small doses fibrillation could not be produced by single shocks of three times the strength which was required to fibrillate the ventricle before drug administration and in the other 11 dogs fibrillation thresholds were elevated. Following injection of larger doses of these drugs despite the prolongation of refractoriness and the decreased excitability, the heart became more susceptible to fibrillation by single stimuli applied during the vulnerable period (Figure 67 see also Gilson, 1939) The dips and the vulnerable period fell later and later in the cycle as refractoriness was prolonged. It was found that after initial injection of these alkaloids supplementary intravenous injections of 0.5 mg or more of the veratrum alkaloids occasionally produced a slow fibrillatory process in the ventricle which could be abolished by countershock. These drugs definitely do not abolish fibrillation once it has been established (Krayer et al., 1955)

More definite information was obtained when a study was made of the action of veratrine on the transmembrane potentials of mammalian hearts The changes in intrinsically originating and extrinsically induced action potentials were very definite. In these latter experiments transmembrane potentials of auricular and ventricular cells of the dog and rat heart were recorded by glass capillary electrodes with a tip diameter of less than one micron In preparing the tissues for study the heart was excised quickly from the anesthetized animal and the desired portions of muscle excised and immediately immersed in appropriate modifications of Tyrode solution. This bathing solution was maintained at 37° C. and aerated with a mixture of 95% oxygen and 5% carbon dioxide In the earlier experiments of this series veratrine alkaloid (S B Penick & Co) was used and subsequently the alkaloid cevadine was employed. The results obtained with the two however were practically the same

Veratrine produces two distinct changes in the behavior of the cardiac



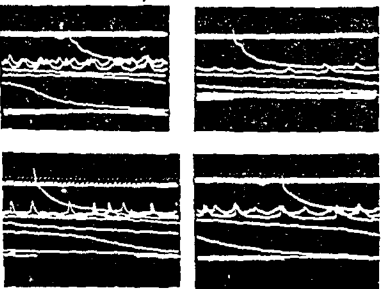


FIGURE 68 At *left* effect of veratrine on the dog auricle showing change in excitability and vulnerability (||||||||) Control (•—•) 0 8 mg per kg (o o) 1·6 mg per kg (Δ Δ)

At right, action of veratrine on spontaneous transmembrane action potential of rat auricle Each of the four pictures shows a single long continuing action potential with its initial rising phase and overshoot, a long slow phase of repolarization each showing a period of partial depolarization (oscillation) and finally a relatively rapid terminal phase of repolarization

muscle in terms of membrane potential. One is marked prolongation of repolarization, and the other is an increased tendency to spontaneous and repetitive activity Both of these changes were observed in all the hearts tested in auricles as well as in ventricles The prolongation of repolarization occurs first in the final portion of the recovery limb of the action potential subsequently the repolarization becomes progressively slower and longer lasting following the initial spike-like depolarization (Figure 67 and 68) The degree of such prolongation depends upon the concentration of veratrine, higher concentrations acting more rapidly and producing more marked prolongation During the phase of prolonged repolarization produced by action of veratrine there often occurs a plateau like portion with a slight slope terminating in a final phase of quick repolarization

In addition to the prolongation of repolarization veratrine increases the tendency to spontaneous firing of the heart muscle This spontaneous activity occurs in preparations of both rat and dog hearts The rhythm of the spontaneous firing is somewhat irregular with an average rate of 30 to 60 or more per minute. Each excitation occurs at a time when repolarization of the preceding action potential is almost completed The spontaneous activity appears in runs lasting from a few seconds to several minutes

The rat's heart is much more sensitive to veratrine than that of the dog In the latter five to ten times the concentration of the drug is required to produce the same degree of change. In the rat, while repolarization normally requires 50 to 100 msec veratrine prolongs it to 5 or 10 seconds or even more. In the dog on the other hand, the normal repolarization phase lasting 200 to 250 msec is prolonged by veratrine to only 5 or 6 seconds Rat hearts show in addition to the changes described above a characteristic type of spontaneous depolarization i e a repetitive oscillation in membrane potential or a repetitive spike that appears during the prolonged phase of repolarization. This type of spontaneous activity is brought about more easily when following the exposure to higher concentrations of veratrine, the tissue is washed by fresh Tyrode solution In the dog a similar tendency to spontaneous activity of this type is observed this is particularly true when high concentrations of these alkaloids are employed

Stimulation during various phases of veratrine-prolonged repolarization results in variously graded electrical responses the responses to stimuli

placed earlier in the cycle being smaller In some experiments on rats a second single stimulus given at a definite interval during the repolarization process is followed by multiple firing, while stimuli at other intervals produce only a single response Veratrum alkaloids not only cause changes which render the heart and its individual cells vulnerable to fibrillation by applied stimuli but also cause a periodic spontaneous intrinsic origin of fibrillatory activity A combination of slowed conduction and an imbalance of effects on the excitability and refractoriness of various cardiac cells may explain the increased vulnerability of the heart following administration of this drug

THE EFFECTS OF SYMPATHOMIMETIC AGENTS The effects of epinephrine and nor epinephrine were compared in a series of experiments on the vulnerability of the *ventricular* myocardium Hearts were driven at

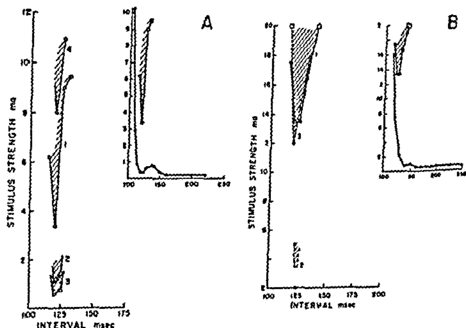


FIGURE 69 A Insert demonstrates relationship of vulnerable period to strength interval curve under control conditions Graph depicts the effect of l-epinephrine on fibrillation thresholds 1—just prior to 2—1 minute 3—2 minutes and 4—5 minutes following injection of 2.5 ml. of a 1 25 000 dilution within a 2.5 minute interval.

B Effect of l nor-epinephrine on ventricular vulnerability Conventions as in A. 1—just prior to 2—2 minutes and 3—4 minutes after injection of 1.85 ml. of a 1 25 000 dilution within a 1 5 minute interval Extras ( ), Multiples (o) (Hoffman et al., Circulation Research, 1955)

a rapid rate during control tests so that ventricular escape from the drive stimuli would not occur following injection of either agent. In all cases bilateral section of the cervical vagi was performed to prevent A V block during the period of hypertension resulting from either drug (Hoff and Nahum, 1934, Lenel et al., 1948 Hoffman et al 1955)

The chloride salts of l-epinephrine and l nor-epinephrine at a dilution of 1 25 000 were injected into the external jugular vein by means of a mechanically driven syringe The injection rate of these solutions was varied in different experiments from 0.5 to 4.5 ml/min and the total volume injected varied from 0.5 to 10 ml. An interval of 1 to 1½ hours elapsed between injections in most experiments

1 *The effects of l-epinephrine on vulnerability* The injection of l-epinephrine had a consistent and profound effect on the vulnerability of the ventricle to single test stimuli (Hoffman et al, 1955) As seen in Figure 69 A when a 1 25 000 solution was injected at a rate of 1 25 ml/min, the minimum fibrillation thresholds were often lowered to levels only slightly above the threshold for a single response. Lowest thresholds were obtained from 1 to 3 minutes after the start of injection Subsequently, greater difficulty in producing fibrillation was encountered even to the extent that the heart became less vulnerable than before drug administration In most animals this period of lessened vulnerability persisted from 10 to 30 minutes prior to the return to control values

With slower rates of injection (0.5 to 0 7 ml/min) although the early enhancement of vulnerability was reproduced the second phase that of diminished vulnerability was greatly decreased or absent. Of some interest was the observation that, even when the injection period was prolonged up to 10 minutes the phase of lowered fibrillation thresholds lasted only 2 to 3 minutes A similarly transient change characterizes the effect of epinephrine on resting excitability (see Chapter VIII) This reversal of action of epinephrine has also been reported by others (Wegria and Nickerson, 1942)

2. *The effects of l-nor-epinephrine on vulnerability* L-nor-epinephrine when injected in the same concentration and at the same rate as epinephrine produced similar changes in vulnerability As seen in Figure 69 B fibrillation thresholds were lowered markedly *immediately* following the start of injection and, after 2 to 3 *minutes* returned to control values With more rapid rates of injection a period of decreased vulnerability followed just as in the case of epinephrine.

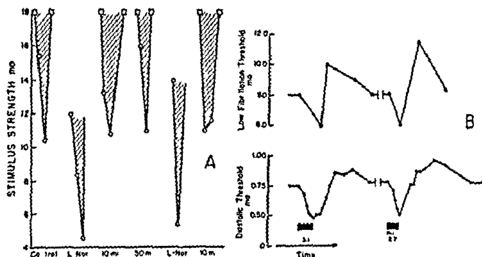


FIGURE 70 A The effect of repeated injections of l nor-epinephrine on ventricular vulnerability demonstrating reproducibility of effect Conventions as in figure 69 Dose 2.5 ml of a 1 25 000 dilution within 2 minutes

B Comparison of effects of l epinephrine and l nor-epinephrine on diastolic thresholds and lowest fibrillation threshold in the same dog Dose l-epinephrine 3.5 ml l nor-epinephrine 2 7 ml (Hoffman *et al* Circulation Research 1955)

With both amines, the effect of a single dose was quite constant in a given animal Even repeated administration produced no permanent change *in the control values (Figure 70 A)*

3 *Relationship between fibrillation thresholds and resting excitability* In most experiments there was a close temporal correspondence between the effect of the sympathomimetic amines on the level of resting excitability (see Chapter VIII) and on the fibrillation thresholds As demonstrated in Figure 70 A and 70 B and Table 12, the period of maximum vulnerability corresponds closely to the period of maximum lowering of diastolic *thresholds Similarly the period of decreased vulnerability* was more or less coexistent with the elevation of diastolic thresholds above control values

The correlation *between the magnitude of change in the fibrillation* and diastolic thresholds was less exact The per cent change in each of these variables at different times after injection is shown in Table 12 While in some cases the magnitude of change in both is *remarkably similar* in other instances a large change in one is accompanied by a minor variation in the other It is likely, however, that these results are at least in part due to the testing technique since the simultaneous *determination*

TABLE 12.—*Time of Maximum Change in Thresholds and Vulnerability Following Drug Administration*

Date of Exp	Test N	Drug	%Δ Threshold	% Δ Fib Threshold	Dose ml	Injection rate ml/min	Time after start of injection min
5/8/53	1	Nor	−25	−80	1.85	1.25	+2
			−32	−55			+3
			−12	0			+10
7/7/53	1	Nor	−15	−11	2.5	1.25	+2
			+5	+40			+30
	2	Epi	−14	−15	4.5	2.25	+1.5
			−3	−5			+15
			+22	+36			+22
			+4	+10			+35
	3	Nor	−20	−28	4.5	2.25	+2
			−1	+24			+14
			+4	+24			+20
7/8/53	1	Epi	−33	−15	1	1	+2.5
7/10/53	1	Epi	−17	−25	10	1	+1.5
			+1	+6			+10
7/17/53	1	Epi	−37	−12	4.2	4.2	+1.75
			−25	−22			+3.0
9/29/53	1	Epi	−34	−33	2.2	1.1	+1.5
			−2	+12			+6
11/23/53	1	Nor	−21	−20	2.2	1.1	+2
2/2/54	1	Epi	−33	−23	3.1	1.8	+2.5
			−20	+17			+10
			+13	+30			+15
			+4	+5			+30
	2	Nor	−3	−25	2.7	1.3	+2
			−6	+6			+5.5
			+10	+40			+17.5
			+2	+2			+22.5
	3	Nor	−40	−12	4.4	1.5	+4
			0	−14			+12
			0	+21			+39
	4	Epi	−36	−26	3.4	1.2	+3
			+20	+36			+15
			+2	+18			+42

Epi=l-epinephrine, 1:25 000
Nor=l nor-epinephrine 1:25 000

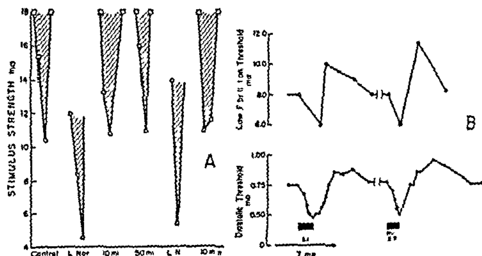


FIGURE 70 A The effect of repeated injections of l nor-epinephrine on ventricular vulnerability demonstrating reproducibility of effect Conventions as in figure 69 Dose 2 5 ml of a 1 25 000 dilution within 2 minutes.

B Comparison of effects of l-epinephrine and l nor epinephrine on diastolic thresholds and lowest fibrillation threshold in the same dog Dose l-epinephrine 3.5 ml l nor-epinephrine 2 7 ml (Hoffman *et al.*, Circulation *Research*, 1955)

With both amines, the effect of a single dose was quite constant in a given animal Even repeated administration produced no permanent change in the control values (Figure 70 A)

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shown that these drugs have similar though less marked effects on cardiac excitability when changes in blood potassium level are prevented (Siebens et al., 1953) In addition, it has been noted (Chapter VIII) that the administration of either of these sympathomimetic agents causes only a small decrease in the duration of refractoriness and a fairly marked increase in intraventricular conduction velocity The possible relationships between all of these alterations in cardiac excitability and the marked increase in vulnerability resulting from epinephrine and nor-epinephrine will be discussed subsequently

THE EFFECTS OF ACETYLCHOLINE AND VAGAL STIMULATION

The effects of vagal stimulation and of acetylcholine on the vulnerability of the *auricular* myocardium were studied both in intact hearts and in isolated preparations of auricular muscle. The details of the methodology

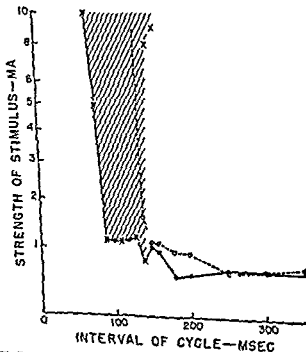


FIGURE 71 Effect of vagal stimulation on vulnerability of the dog auricle. Control strength interval curve (o——o) No vulnerability was found under control conditions. Cross-hatched area shows vulnerability during vagus stimulation threshold strength-interval curve during stimulation (•—•) fibrillation at threshold (x——x) (Hoffman et al., Amer J Physiol, 1952)

of the fibrillation and diastolic thresholds was impossible Thus, at least during the time when excitability was changing rapidly, similar conditions in the myocardium may not have obtained at the time the two measurements were made

4. *Effect of rate of injection* Earlier studies of the effect of epinephrine and nor epinephrine on the excitability of the dog ventricle (Siebens et al, 1953) demonstrated that the change in diastolic threshold produced by these drugs was dependent upon the rate of injection of the test solution Slow injection produced a slight fall in threshold with a prompt return to normal, more rapid administration gave rise to a more pronounced fall followed by a persistent rise to levels well above the control values It was of interest to attempt to determine whether this same relationship obtained in the case of fibrillation thresholds and a number of experiments were performed with this objective However, the very limited duration of the early drug effect and the difficulty encountered in measuring the lowest fibrillation threshold made an exact quantitative relationship between rate of injection and magnitude of effect impossible to obtain It was possible, however, to establish that more rapid injection of either epinephrine or nor epinephrine gave rise to a greater lowering of the fibrillation thresholds than did less rapid injections In a number of experiments with both agents, sufficiently slow injection failed to produce any detectable increase in vulnerability In addition, the phase of increased resistance to fibrillation rarely followed slow administration and almost always accompanied the elevation of diastolic thresholds that resulted from rapid injection

5 *Comparison of l epinephrine and l nor epinephrine* In a number of experiments the effectiveness of similar doses of both epinephrine and nor epinephrine was compared in the same animal As shown in Figure 70 and Table 12, both sympathomimetic drugs had similar qualitative and quantitative effects with respect to both the early phase of enhanced vulnerability and the subsequent phase of elevated fibrillation thresholds Furthermore, there was no difference between these amines either in the frequency with which fibrillation followed their use nor in the ease of defibrillation by means of countershock

As stated in a previous chapter, the changes in diastolic thresholds (decrease and increase) resulting from epinephrine are always associated with marked changes in the level of serum potassium (increase and decrease, respectively) Thus the changes in vulnerability can be related to variations in the blood concentration of this electrolyte although it has been

cause fibrillation. Local application of acetyl β methylcholine (Nahum and Hoff 1940) and acetylcholine (Scherf and Chick, 1951) to small areas of the auricle produce auricular fibrillation These drugs likewise cause fibrillation if added to the fluid bathing isolated auricles (West et al, 1954) or to the circulation in heart lung preparation (Burn et al., 1955) Other vagomimetic drugs are known to have a fibrillation producing action (Cautrelet and Halpern, 1932) The shortening of the refractory period which permits driving of the heart at a more rapid rate (De Elio 1947), the slowing of conduction in the auriculo-ventricular node associated with facilitation of conduction in the auricle and the varied effects on pacemaker activity (DiPalma and Mascatello 1951 Burn 1954) suggest that the increased susceptibility to fibrillation caused by acetyl choline or vagus action is due to a mixture of effects some of which are inhibitory while others are excitatory in nature.)

OTHER DRUGS WITH A DUALITY OF ACTION Numerous other drugs have fibrillatory and antifibrillatory effects. There seems to be no structural specificity associated with fibrillatory or antifibrillatory action (Van Dongen 1936 DiPalma and Schultz 1950, Moe and Mendez, 1951 Brown et al 1951 Dawes 1952 Winbury and Hemmer 1955) It has been reported that α fagarine (allocryptopine) will raise fibrillatory thresholds and prevent fibrillation after ligation of coronary arteries (Moisset de Espanes and Navarro 1938) It will stop aconitine induced auricular fibrillation and flutter (Scherf 1948) Papaverine has somewhat the same effects but it has been found that these drugs may also provoke fibrillation even in the ventricle (Elek and Katz 1942 Wegria and Nickerson 1942)

A great deal has been written concerning digitalis-induced arrhythmias (Wegria et al 1941 Enselberg et al., 1951 Goodman and Gilman 1955), the protective action of potassium (Sampson et al 1943 Lown et al, 1953 Garb and Venturi 1954) and the potentiating action of calcium (Baker and Baker 1955) on this digitalis effect. Studies of the action of cardiac glycosides on single ventricular fibers (Woodbury and Hecht, 1952) have shown that digitoxin ouabain and strophanthidin in extremely high concentrations accelerate repolarization thus shortening the membrane action potential as do some of the other drugs which have the ability to increase vulnerability It can be said that in the case of all these drugs there is evidence of potential mixed actions which might eventuate in a dissymmetry of response and the production of arrhythmias

employed have been described in a previous chapter (VIII) and will not be repeated The results obtained were as follows

Activation of either or both *vagus nerves resulted in a marked shortening* of the absolute refractory period of the auricle This was accompanied by a decrease in total refractoriness of greater or lesser extent, depending on the strength of vagal stimulation During this marked change in refractoriness, there *was no change in the level of resting excitability* and only a slight increase in conduction velocity At this time there was noted a great increase in the vulnerability of the auricle to fibrillation induced by single test shocks As seen in Figure 71, not only were thresholds for *fibrillation decreased, but the duration of the period of vulnerability was* greatly prolonged In some experiments fibrillation was the only response which could be obtained with just threshold stimuli during the entire relative refractory period and at times suprathreshold shocks resulted in *this arrhythmia even when applied late in diastole long after* the full recovery of excitability When long lasting fibrillation occurred, additional vagal activation shortened the f f interval and often, after the cessation of vagal activity, regular rhythm was promptly resumed A brief period of overshooting of control values of excitability, refractoriness, etc was encountered at the end of vagal stimulation but because of the limited duration of this overshoot no tests of vulnerability could be made before *normal excitability was restored*

The effects of injected acetylcholine on the transmembrane potentials of the isolated auricle have been described in Chapter VIII During the time when the duration of the action potential was *markedly shortened* very rapid spontaneous rhythms were often encountered These arrhythmias were most often regular, but at times a distinct irregularity in rate of firing was evident Moreover, even during regular activity there were *often short bursts* of action potentials at irregular rhythms This spontaneous activity was not associated with a change in the resting transmembrane potential of the individual fibers, a finding which might be anticipated *from the lack of effect of acetylcholine on the resting thresholds* of auricular muscle

In conclusion it can be stated that stimulation of the vagus may result in stoppage of auricular fibrillation but *also increases vulnerability* Acetylcholine and vagus stimulation accelerate the rate of fibrillation (Rosenblueth, 1953) and may have a defibrillatory action but when administered to a non fibrillating heart it *increases vulnerability and may*

rather a marked shortening in the duration of refractoriness. The slight increase in conduction velocity also noted is probably of little importance in this consideration Moreover hypothermia, which usually increases the duration of refractoriness, elevates thresholds and slows conduction also greatly increases the vulnerability of the ventricle to fibrillation (Chapter VII) An increase in the concentration of extracellular potassium on the other hand (Chapter X) is known to shorten refractoriness slow conduction and, at the concentrations under consideration elevate thresholds during diastole These same effects are also associated with a marked increase in vulnerability to fibrillation.

If stability of the membrane of heart cells and changes in their transmembrane potentials are considered in addition to the usual measurements of excitability several other observations are worthy of mention Weidmann (1955) has shown that the membrane of heart cells is stabilized by quinidine procaine amide and antihistaminics drugs which tend to prevent fibrillation (see also Fleckenstein and Hardt, 1949) Neither the resting potential nor the amplitude configuration and duration of the action potential, once it has been elicited, are affected This same technique of studying cellular states and responses has been employed in endeavors to determine the effects of a number of factors known to increase the vulnerability of the myocardium to arrhythmias (high and low potassium, high and low calcium epinephrine acetylcholine) Both extremes of potassium concentration are associated with a partial depolarization so that the resting transmembrane potential is quite close to the critical (threshold) level of depolarization at which spontaneous activity ensues On the other hand, while low calcium increases the absolute magnitude of this critical potential and high calcium has the opposite effect, in neither case is the resting potential changed markedly and in the latter the effect is actually one of stabilizing the membrane Similarly, the effects of acetylcholine on isolated single fibers have been shown to cause little alteration in the level of the transmembrane potential. Thus just as in the case of the excitability studies, no uniform action on either the resting potential or critical "threshold" potential can be ascribed to these several agents which are prone either to cause fibrillation or enhance vulnerability It can be said however that the antifibrillatory agents found to be most satisfactory do have a stabilizing effect on the cardiac cell membrane This is important to antifibrillatory action in that it would tend to reduce the stimulating effectiveness of electrotonic current flow at a

THE MODE OF ACTION OF FIBRILLATORY AND ANTIFIBRILLATORY AGENTS

In beginning a discussion of the mode of action of fibrillatory and antifibrillatory drugs one of the first statements which should be made is that the allocation of drugs to such categories must be qualified In high concentrations and under certain circumstances quinidine and other of the antifibrillatory agents may actually increase vulnerability to fibrillation, the initial effects of epinephrine are such as to increase vulnerability but later there is actually a reduction of vulnerability to fibrillation by electrical stimuli, other drugs in doses which decrease excitability, prolong the refractory period and actually raise thresholds to fibrillation by electric shock, nevertheless have an effect which sensitizes the heart to fibrillation by action of other drugs given concurrently

It should be stated also that the studies reported in this chapter do not demonstrate a definite and uniform relationship between changes in various parameters of excitability which result from a given antifibrillatory compound and the magnitude of the protection afforded either the auricle or ventricle against multiple firing or fibrillation However, the results obtained do permit certain conclusions to be drawn and also certain hypotheses to be advanced

To deal first with the factors which might be related to the production of fibrillation or multiple firing, the various theories which previous workers have advanced are discussed in Chapter VI With respect to the initiating event, the studies reported here on the effect of sympathomimetic agents are suggestive It has been noted that the phase of enhanced vulnerability produced by epinephrine and nor epinephrine coincides closely in time with a dramatic increase in the level of resting excitability and the intrinsic excitatory processes (rate of beat), the subsequent diminution in vulnerability is similarly associated with a decrease in resting excitability, although in this case the temporal correspondence is less exact The fact that both epinephrine and nor epinephrine cause a slight decrease in the duration of the refractory period is less impressive in view of the concurrent increase in conduction velocity It is thus tempting to conclude that the level of resting excitability is the parameter of excitability most closely related to production of vulnerability to fibrillation On the other hand, it has also been demonstrated that vagal stimulation produces a great increase in the vulnerability of the dog auricle to fibrillation In this instance, however, there is *no* change in diastolic excitability, but

tection from both experimental and clinical arrhythmias Moreover, especially in the studies of the SKF compounds no consistent relationship has been found between protection against arrhythmias and changes in either refractoriness or diastolic excitability

If any single conclusion is warranted on the basis of these studies it is as follows Any factor which results in a disproportionate change in the several aspects of cardiac excitability is likely to increase vulnerability to arrhythmias Of all the changes produced by the antifibrillatory compounds studied it is the elevation in diastolic thresholds (or decrease in resting excitability) which seems most closely related to protection from fibrillation Whether this decreased excitability, in turn, results directly from a change in resting membrane potential, a "stabilization" of the membrane a change in the critical "threshold" potential, or from some other factor as yet unknown cannot be said However in selected cases it remains a distinct possibility that prolonged refractoriness or slowed conduction might be a sufficient change to produce the observed alteration in vulnerability The concept that a disproportionality of change in various tissues of the heart may be responsible for disorganization of action and fibrillation is supported by the well known fact that localized application of drugs or cold or local injury often produce fibrillation More will be said about selective sensitivity of different parts of the heart in the following chapter

Consideration of the multiplicity of factors and influences which might disorganize the action of the heart causes one to be more impressed by the ability of the heart to maintain its normality of function than by the fact that fibrillation and other arrhythmias can be produced.

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distance thereby abolishing saltatory conduction and reentry by confining propagation to spread through adjacent and more normal pathways of conduction

The conclusion that fibrillation may result from multiple causes is not surprising, in light of the demonstration that (Chapter VI) during fibrillation of either the auricle or ventricle the pattern of activity in the individual fibers may be quite different, depending upon the initiating agent. In some cases the single units fire off at a slow and rather regular rate, while in others the single fiber activity is grossly irregular with respect to both rate of firing and amplitude of each action potential The activity of single cells may actually be disorganized to such a degree that segments of the cell became active while other segments are either depolarized or quiescent Disorganization of activity in single cardiac cells can be considered the ultimate degree of fibrillation It appears that *minute subdivisions of the cardiac cell membrane and its associated contractile tissue retain the capacity of originating activity and responding independently of other elements An antifibrillatory drug must somehow protect coordinating influences at work in a cell and this cannot be directly determined by measurements of transmembrane potential or excitability Thus one is forced to conclude that, while there may be some common initiating agent for all arrhythmias, its nature is not necessarily revealed by the type of information available at present Similarly no one antifibrillatory action has as yet been found*

One additional point is worthy of mention at this time A cell can be said to possess a relatively high degree of stability, in terms of resistance to stimulatory influences, when it is in either of two states 1) when it is completely depolarized and before significant repolarization has begun and 2) when the membrane is fully polarized and being maintained in this condition by a normal balance of factors The cell can be said to be in an unstable situation when its membrane potential is in an intermediate state

Since it is not possible to find a single factor or combination of factors uniformly associated with increased vulnerability, the results reported for the various antifibrillatory agents are more readily accepted While, in the case of quinidine, there are changes in both refractoriness and diastolic excitability which might protect against fibrillation according to the classic concept of Lewis (1925), Lewis and Drury (1926), procaine amide produces little change in ventricular refractoriness but affords good pro

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X The Effect of Inorganic Ions on Cardiac Excitability

The actions of an excess and a deficiency of K Na Ca and other ions on cardiac excitability conduction membrane potential refractoriness and vulnerability to fibrillation are described and discussed The mechanism of action of these ions on transmembrane potentials is considered

PROFOUND ALTERATIONS in the rhythmicity, conductivity and excitability of the human heart are frequently encountered as a result of only moderate alterations in the electrolyte pattern of the blood and thus an understanding of the effect of inorganic ions on heart muscle is of considerable importance in any study of cardiac function It has already been pointed out (Chapter II) that the maintenance of normal transmembrane potentials in resting cells requires a very definite partition of ions the initiation and propagation of excitation in cardiac muscle as well as in nerve and skeletal muscle cells involve an ionic flux. Calcium and potassium im balance in particular greatly affect the permeability, the excitability and the responses of all cardiac tissues The absence or over abundance of other ions likewise results in abnormal states and reactions of the heart.

The dependence of normal heart action on the presence of certain inorganic ions in proper concentration has been appreciated since the early studies of Ringer (1880-82 1882-83-a and b, 1886) Clark (1912, 1913) and others (Locke 1900 1901 Locke and Rosenheim 1904 Lovatt Evans 1912) Ringer demonstrated that three cations Na^+ K^+ and Ca^{++} are essential constituents of any perfusion fluid if it is to support contraction for more than a few moments. The only essential anion is Cl^-, although HCO_3^- and $PO_4^=$ are beneficial, as is the inclusion of Mg^{++} and Dextrose in the fluid medium when prolonged activity is desired

Early myographic studies of perfused frog hearts clearly demonstrated the major effects of the three essential cations on rate rhythmicity, and contractility (Ringer 1880-82 1882 83 1886) A heart perfused with a solution of 0 75% NaCl rapidly becomes hypodynamic and after a brief interval all mechanical activity ceases Addition of Ca^{++} to the perfusion fluid results in a temporary restoration of contractions but relaxation after

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CHANGES INDUCED IN MEMBRANE RESTING POTENTIAL The effect of potassium has been studied in auricle ventricle and Purkinje fibers of the mammalian heart. In the case of the cat auricle, Burgen and Terroux (1953-a) has shown that the depolarization resulting from an

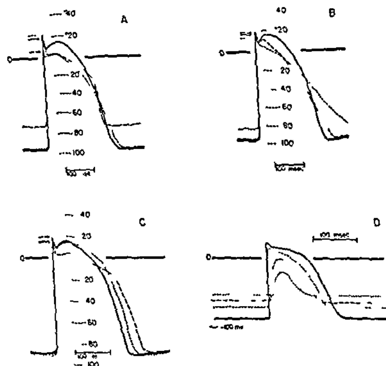


FIGURE 72. Tracings of papillary muscle transmembrane action potentials showing the effects of Ca^{++} and K Control (———) time and voltage calibrations shown in figures.

A Low calcium (0.27 mM) in the presence of low potassium [0.67 mM ( )] and high potassium [8.1 mM (— — — —)]

B. High calcium (8.1 mM) in the presence of low potassium [0.67 mM ( )] and high potassium [8.1 mM (— — — —)]

C. Effect of changes in concentration of calcium alone Potassium=2.7 mM Ca^{++}=0.27 mM ( ) and 0.027 mM (— — — —)

D The progressive effect of high potassium (13.5 mM) in the presence of normal calcium reducing *resting* potential and height of action potential. Smallest action potential ( ) not propagated.

Arrows indicate height of reversal of action potential in each case.

each systole becomes less and less complete until again activity ceases with the heart muscle remaining in a shortened condition At this stage the addition of K^+ once more results in the onset of regular contractions and this activity is maintained for a reasonably long period It has also been determined that the relative concentrations of Ca^{++} and K^+ are of great importance as well as the absolute concentration of each ion A relative excess of Ca^{++}, even in the presence of K^+, produces a so called systolic arrest, while a relative K^+ excess results in a gradual diminution in the strength of contraction until no systolic force is developed

Subsequent and more meticulous studies have greatly extended our knowledge of the role of ions in maintaining normal mechanical activity in cardiac muscle (Schutz, 1936, Garb, 1951 a and b, Green et al, 1952, Szent Györgyi, 1953) These studies of contractility will be considered in the succeeding chapter For the present, discussion will be restricted to the effects of inorganic ions on the electrical activity and excitability of the mammalian heart.

POTASSIUM

Extensive studies have been made of the effect of changes in the concentration of potassium on all aspects of cardiac function both in induced alterations in experimental animals (Harris and Madjerek, 1948, Garb, 1951 a and b, Hajdu, 1953) and also in spontaneous variations encountered as a consequence of disease states in man (see Lepeschkin, 1951) Small changes in the level of K^+ have profound effects on excitability and electrical activity of both isolated and in situ hearts, especially when the level of Ca^{++} remains constant In man an elevation of K^+ from the normal range of 4-5 millequivalents per liter to 8 10 millequivalents results in slowing of the heart A V block marked slowing of intra ventricular conduction and pronounced electrocardiographic changes In addition, there is a decrease in the force of ventricular systole due to both the fractionation of contraction and the direct effect of K^+ on the contractile mechanism of cardiac muscle Equally severe but somewhat different disturbances result from an equivalent depression of the serum K^+ level

The mechanism by which most of these functional abnormalities are produced can be explained on the basis of the effect of this ion on electrical properties of the cardiac fiber membrane, and the role of membrane phenomena in spontaneous rhythmicity, conduction, and the genesis of the electrocardiogram

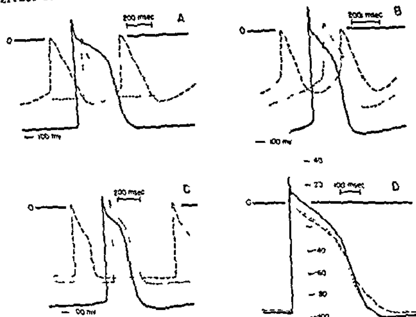


FIGURE 73 Tracings of Purkinje fiber transmembrane action potentials. Control Ca^{++}=2.7 and K = 2.7 mM (———) time and voltage calibrations indicated in figures.
A. High [K = 13.5 mM ( )] and low [K = 0.35 mM (– – – –)] when Ca^{++} is normal (2.7 mM)
B Ca = 8.1 and K = 0.68 mM (– – – –) CA = 2.7 and K = 0.68 mM ( )
C. Ca^{++} = 2.7 and K = 8.1 (– – – –) Ca^{++} = 8.1 and K = 8.1 (– – – –)
D K = 2.7 and Ca^{++} = 10.8 mM (– – – –) K = 2.7 and Ca^{++} = 0.27 mM ( )

be stimulated is increased. If on the other hand the resting potential falls below a certain level excitation can no longer be produced by stimuli other than those which first cause a transient hyperpolarization of the fiber membrane This relationship between resting potential and threshold in the case of skeletal muscle has been extensively studied by Jenerick and Gerard (1953)

In view of this relationship it is to be expected that the effect of potassium on the excitability of the heart to applied stimuli will depend on both the initial level of the membrane potential and the magnitude of the change in K concentration Thus if the level of potassium is slowly elevated in the intact dog from a normal value of 3 mM to 10-12 mM the threshold is first decreased (as a result of partial depolarization) and

increase in the extracellular K^+, above certain limits, is a linear function of the concentration of this ion, a ten fold increase resulting in a drop in resting potential of about 35 mv This relationship is to be expected from the known effect of K^+ on resting potential discussed in Chapters II and V On the other hand, when the level of extracellular K^+ is decreased below 5 6 mM/liter, the expected increase in resting potential fails to occur *Quite to the contrary*, if the level of K^+ in the extracellular fluid is lowered markedly there is again a decrease in resting potential (Burgen and Terroux, 1953 a) Furthermore, as is true of other aspects of cardiac function, the effect of K^+ on resting potential is partly dependent upon the simultaneous level of Ca^{++} In the case of the dog ventricle (Hoffman and Suckling, 1955), *the depolarizing effect of low potassium can be diminished* by a simultaneous decrease in Ca^{++} and the effect of elevated K^+ can likewise be partly reversed by a simultaneous increase in calcium levels This interrelationship is shown in Figure 72 When the concentration of Ca^{++} in the extracellular fluid is 0 27 mM/liter, a potassium concentration of 8 0 mM lowers the resting transmembrane potential from 90 mv to approximately 70 mv On the other hand, if the level of Ca^{++} is elevated to 8 1 mM the resting potential is restored to a normal value of 95 mv Similarly, with a Ca^{++} concentration of 8 1 mM the resting potential falls to 82 mv when K^+ concentration is 0 7 mM, lowering the calcium to 0 27 mM restores the resting potential to normal Similar results obtained with isolated Purkinje fibers are shown in Figure 73

These findings, in addition to the observation (Burgen and Terroux, 1953 b) that the *presence of acetylcholine alters the level of resting* potential resulting from a given potassium concentration, strongly suggest that the resting potential of cardiac muscle is not a simple diffusion potential resulting from the concentration gradient of K^+ ion *On the other* hand, the effect of K^+ can be predicted, if the Ca^{++} concentration is known, with respect to the change in resting potential that will be produced (Hoffman and Suckling, 1955) In addition, a knowledge of the alteration in resting potential aids greatly in the interpretation of other effects of potassium on cardiac excitability (see below)

CHANGES IN THRESHOLD The effect of changes in the magnitude of the resting transmembrane potential on the excitability of cardiac muscle has been discussed in Chapter V Briefly it can be stated that if the resting potential is lowered towards the critical "threshold" potential, all other factors remaining constant, the ease with which the tissue can

(Weidmann 1955-a) have shown that the capacity of the fiber to undergo an increase in Na permeability is related to the level of membrane potential prior to stimulation Thus if the resting potential is low, the *maximum* sodium current elicited by activity is less than normal. Because of this decrease in inward sodium current, the rate of rise and magnitude of the action potential are both decreased It is thus likely that the action potential changes elicited by potassium are a result of the depolarizing action of the ion The change in duration of the action potential which is also observed is of less certain origin, however, this more rapid repolarization *is frequently* associated with a decrease in magnitude of the action potential regardless of the agent responsible for the latter change. Finally, just as a change in Ca^{++} *influences the* effect of K on resting potential, an elevation of K^{+} antagonizes *the effect of* high Ca^{++} on the duration of the action potential (Figure 72 73)

EFFECTS ON CONDUCTION VELOCITY AND A V DISSOCIATION

One of the most pronounced effects of an elevation in the serum K concentration is a marked decrease in the velocity of impulse propagation This manifestation of potassium intoxication can be *accounted* for on the basis of the changes discussed in the preceding sections In the first place it is a necessary concomitant of the decrease both in *rising velocity* and magnitude of the action potential that the velocity of impulse conduction will be decreased (Katz 1947) This effect can be described in general terms as follows If the magnitude of the depolarization in any area of the fiber membrane is less, the strength of the current flow resulting from this depolarization will likewise be diminished As a result of this lowered density of eddy currents preceding the action potential, the depolarization of adjacent segments will proceed less rapidly and in addition the spread of the eddy currents to more distant regions will be less The effect of both of these factors will be to decrease the conduction *velocity* A complicating factor is the simultaneous decrease in resting *potential which* within certain limits makes excitation more easily attained. At any time the net change in conduction velocity will be a *resultant* of the two changes mentioned and in most instances this *net result* is to diminish the velocity of impulse propagation

Atrio-ventricular dissociation is noted *quite early* in the presence of elevated serum potassium. A *specific effect* on transmission from the auricular muscle to the A V node is the most likely possibility The isolated papillary muscle and auricle *are still* capable of repetitive activity

then abruptly increased until the heart becomes completely inexcitable when excessive depolarization has been produced (see Figure 58) Similarly, a decrease in the K^+ concentration results first in an enhanced excitability and subsequently a depression or complete loss of excitability to stimuli of the usual range of intensity and duration

CHANGES IN SPONTANEOUS RHYTHMICITY A lowering of extracellular potassium concentration, especially when Ca^{++} is at a low normal level, results in an enhanced spontaneous rhythmicity (Figure 73) (Garb 1951 a and b) This increased rhythmicity is shown both by normal pacemakers of the Purkinje system (Weidmann, 1955 b) and also by previously quiescent fibers of isolated papillary muscles Similarly, if the level of extracellular K^+ is increased above normal, spontaneous rhythmicity of some fibers is occasionally enhanced when the level of K^+ is just sufficient to cause a partial depolarization The most frequent effect of high K^+ concentrations, however, is a loss of spontaneous activity due to excessive depolarization (Figure 73) Although changes in potassium level affect the rate of slow diastolic depolarization seen in pacemakers, the enhanced rhythmicity resulting from this agent is also related to the associated change in resting potential which results from changes in the K^+ concentration When the fiber membrane is depolarized to a level near the threshold potential it becomes less stable and repetitive firing of multiple areas is likely to ensue Whether this increase in pacemaker activity results from the effect of lowered membrane potential on membrane permeability (see Chapter V) or on some other aspect of those processes which are normally responsible for maintaining normal polarization is not certain

CHANGES IN THE TRANSMEMBRANE ACTION POTENTIAL The effect of an alteration in the concentration of K on the action potentials of single fibers of papillary muscle and single Purkinje fibers is shown in Figure 72, 73 Similar results occur in the case of the auricle (Burgen and Terroux, 1953 a) It can be seen that the action of this ion is similar in both tissues, elevated K^+ causing a decrease in the rate of rise of the action potential, a decrease or complete loss of the reversal of membrane polarity, and also a shortening in the duration of the action potential The fact that a marked lowering of the potassium concentration results in a similar change in the action potential (Figure 72, 73) suggests that the mechanism by which these effects are produced is related to the change in resting potential and not a direct action of the ion on the excitatory process As has been described in Chapter V, "voltage clamp" studies

be found in conjunction with the subsequent discussion of the effects of calcium on the heart.

CALCIUM

In man disturbances of calcium metabolism much more frequently consist of a lowering of the serum Ca^{++} level rather than an elevation as is the usual case with potassium Furthermore within the range encountered in most disease states even those elevations which do occur are not great enough in magnitude to produce significant cardiac disturbances (Hoff 1955) However in order to understand the physiological role of this agent the effects of both increases and decreases in Ca^{++} concentration must be considered as well as the interrelationships between this ion and the other constituents of the blood plasma

As in the case of potassium, recent studies of the effect of Ca^{++} on the transmembrane potentials of single cardiac fibers provide the most direct determination of the many changes which occur and permit understanding of the changes in excitability and electrical activity which are known to follow alterations in the extracellular calcium concentration Results of such studies will be considered briefly below

THE RESTING POTENTIAL The most complete studies of the effect of Ca^{++} on membrane phenomena of cardiac muscle have been performed with single fibers of the isolated Purkinje system (Weidmann 1955-b) In this tissue an increase in Ca^{++} concentration to four times the normal value for Tyrode solution (2 7mM/1) or a decrease to one quarter the usual concentration has little consistent effect on the resting potential A slight lowering of membrane potential accompanies low Ca^{++} and a similar slight increase is seen in the presence of elevated Ca^{++} levels This apparent stability of resting potential is encountered only within the range of concentrations mentioned As can be seen in Figure 30 of Chapter V a more severe depletion of calcium (approximately 0 27 mM/1) causes a marked lowering of the transmembrane potential even in the Purkinje system (Hoffman and Suckling 1955)

Studies of the isolated papillary muscle (Hoffman and Suckling 1955) have revealed a more marked change in resting potential in the presence of changes in the concentration of extracellular Ca^{++} In this tissue when the potassium level is within the usual range (2 7 mM) resting potentials are only slightly influenced by alteration of Ca^{++} On the other hand, as has been mentioned in the preceding section, the level of extracellular

at a potassium level of 13 5 mM, and single fibers of the Purkinje system at 10 8 13 5 mM (Burgen and Terroux, 1953 a, Hoffman and Suckling 1955) On the other hand, A V conduction in both man and dog is lost at a serum concentration of 8 9 milliequivalents per liter (Hoff, 1955) *This sensitivity of the junctional region to K^+ explains the early onset of A V dissociation*

ELECTROCARDIOGRAPHIC ALTERATIONS The clinician is often first aware of a change in the serum K^+ concentration because of the changes noted in the standard electrocardiogram (Winkler et al, 1938, Ernstene and Proudfit, 1949, McAllen, 1951) Typically, these consist of a decrease in the amplitude of the T wave, A V block of varying degree and a marked increase in the duration of the QRS complex Although changes such as these are not necessarily pathognomonic of an elevated potassium level, and although the magnitude of the change in K^+ concentration cannot always be determined from the electrocardiogram, the findings noted are frequently a reliable guide to the nature of the underlying disturbance in electrolyte balance In view of the changes that are known to occur in the action potentials of single cardiac fibers the alteration in the ECG is not difficult to understand (see Chapter V)

THE PRODUCTION OF ARRHYTHMIAS The many possible mechanisms *by which arrhythmias can be produced in the mammalian heart have been discussed in detail in a preceding chapter* However, it is of interest to summarize the mechanisms by which an elevation of serum potassium can lead to the onset of fibrillation In the first place the increase in intrinsic rhythmicity which results from an elevated potassium concentration is capable of producing one or more ectopic pacemakers in the myocardium Secondly the decrease in conduction velocity will result in a greater tendency for such pacemakers to escape from the dominance of normally initiated activity Perhaps the most potent disorganizing factor, *however, is the occurrence of local blocks due to a greater depolarization of certain areas more sensitive to the effect of this ion* than are other parts of the myocardium This combination of slowed conduction, local blocks, and increased spontaneous rhythmicity provides all the necessary conditions for fragmentation of response, re-entry, and fibrillation

It is known that potassium, which is one of the most potent *fibrillatory* agents for mammalian hearts, is also an effective *defibrillating agent* Discussion of the use of this particular ion *to accomplish defibrillation* will

area of a single isolated Purkinje fiber, as has been described in Chapter V spontaneous activity is seen to be associated with a slow diastolic depolarization. Moderate changes in the concentration of extracellular Ca^{++} (one-fourth to four times normal) have no effect on the *rate* of this slow depolarization Any observed changes in heart rate result solely from the alteration in threshold potential described above and not from a modification of pacemaker function.

On the other hand when the Ca^{++} level is lowered to about one-tenth of the normal value there are profound changes in the pacemaker activity of Purkinje fibers As seen in Figure 74-C and D not only is there a decrease in resting potential but also a marked change in the rate of diastolic depolarization The rate of lo s of membrane potential is greatly augmented and in addition the action potential is diminished in both amplitude and duration Furthermore, at this level of extracellular Ca^{++}

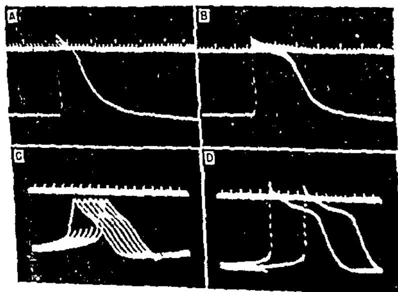


FIGURE 74 Transmembrane action potential from auricular muscle in presence of (A) normal calcium and (B) low calcium. Note the appearance of a plateau in B Time marks in 10 and 50 msec. Pacemaker activity recorded *from* the same area of a *Purkinje* fiber in *low* calcium (C) and normal calcium (D) Time marks in 50 msec. Note difference in amplitude of resting and action potential and rate of diastolic depolarization. (Retouched to show action potential upstrokes by dotted lines.)

Ca^{++} has a pronounced effect on the sensitivity of the resting potential to alterations of the potassium level This effect is such that the depolarizing action of K^{+} is antagonized by high Ca^{++}, and the lowering of resting potential which normally results from a decrease in K^{+} is likewise prevented by a low extracellular Ca^{++} (see Figure 72 and 73) Thus, as has been known for many years, the ratio of the extracellular cations is of as great importance as the absolute concentration of any one

CHANGES IN THRESHOLD High calcium is associated with a decrease and low Ca^{++} with an increase in the sensitivity of the heart to applied stimuli (Garb, 1951 a and b, Green et al, 1952, Weidmann, 1955 b) These changes in excitability might result from many factors, recent studies (Weidmann, 1955 a) have demonstrated that most important is the level of the critical "threshold" potential at which self sustaining depolarization eventuates (see Chapter V) When the excitability of a single Purkinje fiber is determined by means of two intracellular microelectrodes, one to lead in stimulus current and the other to measure potential, the major effect of an increase in the Ca^{++} concentration is to decrease the threshold potential This alteration increases the current strength of stimulus required to excite Similarly, a lowering in Ca^{++} level increases the threshold potential of the single fiber and thus the stimulus requirement is diminished

Changes in excitability resulting from alterations in the level of extracellular calcium are not uniform throughout all parts of the heart When excitability is expressed in terms of the strength of applied stimuli required to elicit a propagated response from specimens of auricle, papillary muscle and Purkinje fiber, it is seen that the specialized tissues and auricle become completely inexcitable at Ca^{++} concentrations which are low but which are still high enough to support normal activity of the ventricular muscle A similar greater resistance of the papillary muscle to increased Ca^{++} concentration is also noted (Hoffman and Suckling, 1955) This selective sensitivity of various tissues to change in calcium concentrations will be discussed in greater detail below

SPONTANEOUS RHYTHMICITY One of the most prominent effects of changes in the level of serum Ca^{++} seen in animals and man is a change in heart rate and rhythm Although many of these variations in rate are the result of extracardiac factors there is also a direct action of calcium on the processes underlying spontaneous rhythmicity in cardiac muscle When transmembrane action potentials are recorded from a pacemaker

in a prolonged positive after potential similar in shape to that normally recorded from skeletal muscle (see Figure 10) The change in the action potential of papillary muscle is of a similar nature The plateau characteristic of the action potential of this tissue is lost and repolarization proceeds with a time course similar to that found in normal auricle (Figure 76)

Low calcium, on the other hand, has quite the opposite effect. The auricular action potential is prolonged and a plateau often appears between the initial reversal and the phase of repolarization (Figure 74-A and B) In the papillary muscle the duration of the plateau is considerably increased the rate of repolarization however is relatively unchanged (Figure 76) As can be seen in Figure 74 B in the presence of low Ca^{++} the auricular action potential is indistinguishable from that of a normal ventricular fiber High Ca^{++}, on the other hand, converts the ventricular action potential to a shape resembling that of a *normal auricular* fiber These findings suggest that the differences normally revealed by these two chambers of the heart may perhaps *include* a difference in Ca^{++} sensitivity of the fiber membranes.

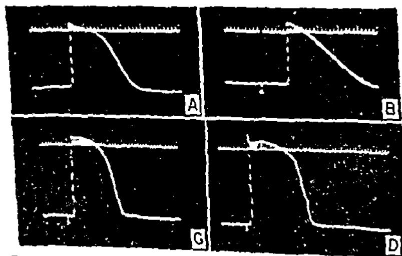


FIGURE 76. Effect of high and low calcium on transmembrane potentials of ventricular tissue A—Control record from a ventricular fiber and B—the effect of a calcium concentration *four* times normal (10.8 mM) C—*Control* record from a different fiber and D—the effect of a calcium concentration *of* one tenth normal (0.27 mM) (Retouched to show action potential upstrokes by dotted lines.)

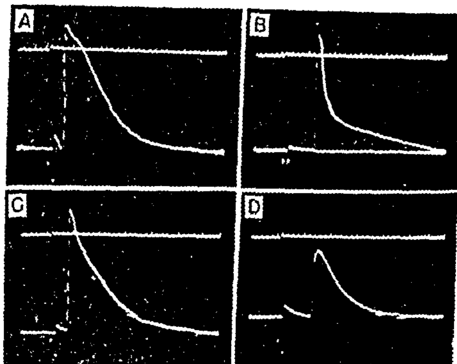


FIGURE 75 Effect of high and low calcium concentrations on transmembrane potentials of auricular fibers A—Control B—Ca =10 8 mM C—Ca =0 65 mM D—Ca =0 27 mM At the high concentration (B) the fiber responds only to alternate stimuli The response in (D) is not propagated Time in 10 and 50 msec. Stimulus artefact before each potential (Retouched to show action potential upstrokes by dotted lines)

diastolic depolarization and pacemaker activity is often recorded from previously quiescent fibers of auricle and ventricle

TRANSMEMBRANE ACTION POTENTIAL Changes in the action potentials indicate, as do the changes in excitability, that there is a great difference in sensitivity of the auricle, ventricle, and conducting fibers to changes in Ca^{++} concentration When the Ca^{++} level is increased to four times normal, the form of the action potential of the Purkinje fiber is *virtually unchanged (Figure 73 C) On the other hand, at a* similar Ca^{++} level the action potentials of auricle and papillary muscle are markedly altered In the case of the auricle (Figure 74-A and B, 75), *added Ca^{++} results in a change in* action potential configuration similar to that produced by acetylcholine The initial stages of repolarization are greatly accelerated, on the other hand, the action potential terminates

results in a great increase in spontaneous rhythmicity not only of the normal pacemakers but also of all parts of the auricle and ventricle Thus low calcium is prone to cause both multiple foci of spontaneous activity and an increase in the ease with which the myocardium can be excited It can be concluded therefore that both increases and decreases in the level of extracellular Ca^{++} create conditions favorable for disorganization and the initiation of fibrillation in each case however the mechanism underlying the arrhythmia is different.

DEFIBRILLATION BY POTASSIUM AND CALCIUM As has been noted in the preceding sections both potassium and calcium are capable of initiating ventricular fibrillation However as has been known for many years (Wiggers 1953), the proper administration of these agents is an effective defibrillating procedure (see Chapter IX) This technique can be described quite briefly as follows. During fibrillation if the chest is open concentrated KCl (5%) can be injected directly into the cavity of the left ventricle If the injection is followed by effective massage of the heart, the potassium will enter the coronary circulation and depolarize the myocardium If *all* fibers are depolarized to an adequate extent, activity will cease throughout the ventricles and fibrillation will be abolished. Continued perfusion of the coronary arterial tree removes the excess K ion and the myocardial fibers will repolarize However, since the condition of the myocardium during recovery from potassium depolarization is also conducive to fibrillation the recurrence of this arrhythmia is quite likely On the other hand, if the injection of KCl is followed by a similar amount $CaCl_2$ the spontaneous rhythmicity of the heart is so depressed that the appearance of multiple pacemakers is much less likely This factor in addition to the direct antagonism between Ca^{++} and K usually results in the restoration of coordinated activity throughout the ventricles With resumption of effective ventricular contractions the coronary flow rapidly restores the extracellular ionic concentrations of the heart to levels at which normal activity is resumed

MAGNESIUM STRONTIUM AND BARIUM

Abnormalities in cardiac function resulting directly from intrinsic alteration in the concentration of magnesium in the blood are not encountered in man (Smith et al. 1939 1942 Engback, 1952) Similarly, the effect of rather wide variations in the concentration of this ion have little effect on the excitability or electrical activity of the isolated heart.

THE EFFECT OF Ca^{++} ION ON SODIUM PERMEABILITY One of the most important actions of Ca^{++} on the function of myocardial fibers is to change the relationship between the level of membrane potential and sodium permeability By means of "voltage clamp" studies (Weidmann, 1955 b), it has been shown that an elevation of calcium concentration increases the ability of the fiber membrane to undergo a change in sodium permeability during depolarization Similarly, the presence of a low calcium level decreases the sodium permeability change resulting from activity The result of these alterations in membrane function is to increase the rising velocity and magnitude of the action potential when the extracellular Ca^{++} is elevated Thus the ability of the fiber to respond and conduct during repolarization is augmented by high calcium levels and diminished by low levels

ELECTROCARDIOGRAPHIC ALTERATIONS The only significant alterations in the electrocardiogram produced by clinically encountered changes in serum Ca^{++}, aside from variations in rate and rhythm, are changes in the duration of the P R and Q T intervals In the presence of a high serum Ca^{++} auriculoventricular conduction is significantly delayed Although this delay may result, in part, from changes in the excitability of the A V node, the most important factor is an augmented vagal activity This effect of calcium on the liberation of acetylcholine is clearly demonstrated by the fact that adequate doses of atropine completely abolish the prolongation of P R interval resulting from an increased Ca^{++} level Changes in Q T interval, on the other hand, are a direct result of the effect of Ca^{++} on ventricular repolarization As described above, the major action of this ion is to change the duration of the plateau of the ventricular action potential without altering the rate of the terminal phase of repolarization These findings are in keeping with the longer or shorter Q T interval and unchanged T deflection recorded during hypo and hyper calcemia

PRODUCTION OF ARRHYTHMIAS When the serum Ca^{++} is elevated to a level three or four times normal ventricular fibrillation is a frequent occurrence The most likely explanation for the production of this arrhythmia is the marked elevation of threshold which is known to result from such a calcium excess A decrease or complete loss of excitability in certain areas of the myocardium will create local blocks and favor re-entry and repetitive activity Also of importance is the different sensitivity of various myocardial areas discussed above Hypocalcemia, on the other hand,

results in a great increase in spontaneous rhythmicity not only of the normal pacemakers but also of all parts of the auricle and ventricle. Thus low calcium is prone to cause both multiple foci of spontaneous activity and an increase in the ease with which the myocardium can be excited. It can be concluded therefore that both increases and decreases in the level of extracellular Ca^{++} create conditions favorable for disorganization and the initiation of fibrillation; in each case however the mechanism underlying the arrhythmia is different.

DEFIBRILLATION BY POTASSIUM AND CALCIUM. As has been noted in the preceding sections both potassium and calcium are capable of initiating ventricular fibrillation. However, as has been known for many years (Wiggers 1933), the proper administration of these agents is an effective defibrillating procedure (see Chapter IX). This technique can be described quite briefly as follows. During fibrillation if the chest is open concentrated KCl (5%) can be injected directly into the cavity of the left ventricle. If the injection is followed by effective massage of the heart, the potassium will enter the coronary circulation and depolarize the myocardium. If *all* fibers are depolarized to an adequate extent, activity will cease throughout the ventricles and fibrillation will be abolished. Continued perfusion of the coronary arterial tree removes the excess K ion and the myocardial fibers will repolarize. However, since the condition of the myocardium during recovery from potassium depolarization is also conducive to fibrillation the recurrence of this arrhythmia is quite likely. On the other hand if the injection of KCl is followed by a similar amount $CaCl_2$, the spontaneous rhythmicity of the heart is so depressed that the appearance of multiple pacemakers is much less likely. This factor in addition to the direct antagonism between Ca^{++} and K usually results in the restoration of coordinated activity throughout the ventricles. With resumption of effective ventricular contractions the coronary flow rapidly restores the extracellular ionic concentrations of the heart to levels at which normal activity is resumed.

MAGNESIUM STRONTIUM AND BARIUM

Abnormalities in cardiac function resulting directly from intrinsic alteration in the concentration of magnesium in the blood are not encountered in man (Smith et al., 1939, 1942; Engbaek 1952). Similarly the effect of rather wide variations in the concentration of this ion have little effect on the excitability or electrical activity of the isolated heart.

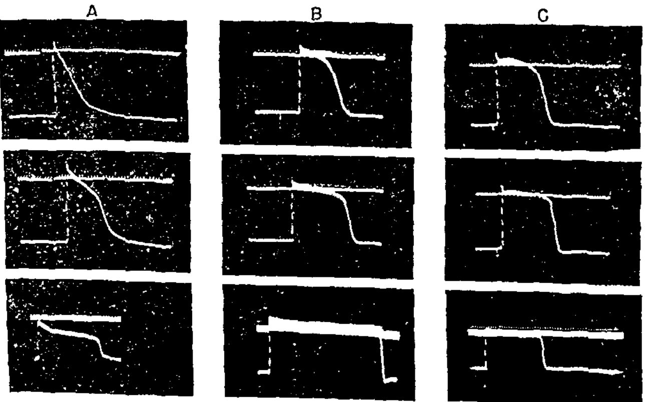


FIGURE 77 The effect of calcium and magnesium depletion on transmembrane action potentials of heart cells The progressive change (top to bottom) produced in auricular fibers (A) and ventricular fibers (B) by prolonged soaking in calcium and magnesium free solution C—Same effect produced in ventricular fibers by a chelating agent (sequestrene) Time marks 50 msec. in lower figures in others, 10 and 50 msec (Retouched to show action potential upstrokes by dotted lines)

On the other hand several striking changes do result from Mg^{++} when the concentration of calcium is decreased.

In the case of the isolated papillary muscle the level of Mg^{++} in Tyrode solution can be increased from 0.5 to 15mM or decreased to zero without markedly changing the form of the action potential or the magnitude of the resting potential. Moreover changes in excitability are light, the highest levels of Mg^{++} causing a slight increase in the threshold If the Ca^{++} concentration is low however, a similar elevation in Mg^{++} often results in a marked decrease in the duration of the single fiber action potential similar to that resulting from a large Ca^{++} excess (Hoffman and Suckling 1953 1955) This similarity of the action of Ca^{++} and Mg^{++} has been known for some time

When the Tyrode solution *is free of both* Ca^{++} and Mg^{++}, furthermore, after one half hour or longer a remarkable *increase* in the duration of the ventricular action potential is noted (Figure 77) This change can be produced quite easily by the administration of Sequestrene (ethylenediamine tetraacetate), a chelating agent with a high *affinity for* calcium and magnesium When both of these ions are completely removed from the extracellular fluid by this means as seen in Figure 81 the plateau of the ventricular action potential is often prolonged from a normal duration of 100-200 msec to as much as several seconds The sub equent addition of Ca^{++} and Mg^{++} restores normal electrical activity suggesting that it is the depletion of these ions rather than some other effect of the *Sequestrene* which produces the changes noted (Hoffman and Suckling 1953)

Strontium, when added to normal Tyrode solution, apparently acts in the same manner as a similar amount of calcium (Garb 1951 b) When the Ca^{++} level is considerably reduced however, the addition of Sr^{++} results in a change in action potential duration similar to that resulting from a complete depletion of Ca^{++} *and* Mg^{++} This finding suggests that when the Ca^{++} level is decreased the Sr^{++} *may* displace the *remaining* Ca^{++} from essential sites on the fiber membrane *The fact that the depletion of both* Ca^{++} and Mg^{++} produces this same change while low Ca^{++} alone does not, also suggests that under certain conditions Mg^{++} may be able to serve the *same function* as Ca^{++} in maintaining normal *excitability* and electrical activity Barium (Kleinfeld et al 1954) on the other hand, increases the duration of the ventricular action potential of the frog heart even at normal Ca^{++} levels

An interesting aspect of these studies is the form assumed by the action

potential during complete depletion of both Ca^{++} and Mg^{++} As seen in Figure 77 the plateau of each action potential is extremely long and yet the rate of spontaneous activity is high As a result, the fiber remains in a depolarized condition almost constantly This finding may be the result of a change in the condition under which the membrane is stable from the normal polarized state to a new condition of stability at a membrane potential near zero

SODIUM AND LITHIUM

Within a range compatible with life of the intact animal the extra cellular sodium ion has relatively little direct effect on the excitability of heart muscle An increase in concentration sufficient to cause death from respiratory failure gives rise to no appreciable changes in either heart rate, regularity of impulse formation, or the force of systolic contraction In addition, cardiac output is maintained until the end Similarly, although there are changes in the force of contraction and in systemic blood pressure, a decrease in serum Na^{+} compatible with life gives rise to little change in cardiac excitability

On the other hand, when isolated hearts are studied, and severe depletion of sodium can be produced, *it is seen that this ion has a profound effect* on electrical activity of heart muscle When osmotic pressure is maintained within normal limits by addition of choline chloride, a marked decrease in extracellular Na^{+} results in a slowing of impulse formation, a decrease in conduction velocity, A V dissociation, and a complete loss of excitability (Clark, 1913) Recent studies of single fibers of the isolated Purkinje system have provided detailed information concerning the nature of these changes (Draper and Weidmann, 1951) As would be expected from the ionic hypothesis discussed in Chapters II and V, a lowering of the extra cellular Na^{+} concentration produces a decrease both in the rate of rise and the magnitude of the transmembrane action potential, this, in turn causes a decrease in conduction velocity In addition, low sodium slows the rate of impulse formation by decreasing the rate of slow diastolic depolarization in pacemaker fibers Below a concentration of 10 20% of normal, spontaneous activity ceases and propagation of the action potential fails These changes are all promptly reversed when the sodium concentration is increased to normal levels As is the case in nerve, Lithium in proper concentration can substitute for extracellular Na^{+} to a limited extent (Weidmann, 1955-c) *Although the changes produced in the action*

potential are profound, alteration of the extracellular Na^+ concentration has little effect on the magnitude of the resting transmembrane potential Similar alterations in the monophasic action potential of the turtle ventricle also occur during depletion of the extracellular sodium ion (Cranefield et al., 1951)

SUMMARY

1 Changes in the concentration of potassium, calcium, and to a lesser extent sodium have a profound effect on the electrical activity and excit ability of the mammalian myocardium.

2. The most pronounced effect of changes in potassium is on the magnitude of the resting membrane potential. Other alterations in cardiac activity associated with an excess or deficiency of this ion can be largely explained on the basis of known effects of the altered resting potential

3 Calcium in excess can be said to increase the stability of the fiber membrane in that rhythmicity and excitability are both decreased. Low calcium has the opposite effect. Other factors of importance are the effect of Ca^{++} on the permeability of the membrane to sodium and also the interrelationship between Ca^{++} and K

4. Marked sodium depletion decreases both the rate of rise and magnitude of the action potential in accordance with the ionic hypothesis of electrical activity Below a certain concentration sodium lack results in a complete loss of excitability Lithium in proper concentrations can substitute for Na to a limited extent.

5 Magnesium has little action in the presence of normal amounts of Ca^{++} when the concentration of this latter ion is decreased, however both Mg^{++} and Sr^{++} have a marked effect on the activity of the fiber mem brane

6 The sensitivity of different parts of the heart, auricle ventricle and conducting system to several of the normal extracellular cations is quite different. This observation is of considerable importance in understand ing the alterations in activity which result from ionic imbalances

7 Most of the changes in myocardial function which are encountered in man in disease states can be clearly explained on the basis of the known effects of these ions on the membranes of cardiac muscle fibers

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XI Mechanical Responses of the Heart and the Excitability Cycle

The mechanical events of the cardiac cycle and their relation to electrical signs of heart action are described Factors influencing mechanical activity and the effect of stimuli placed early in the cycle upon subsequent mechanical responses of the heart are discussed A comparison of the responses of fragments of heart tissue and the total heart is made Summation of contraction and other related matters are considered

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EXCITATION OF THE HEART produces both an electrical and a mechanical response As the *excitatory process is propagated throughout* the heart the associated depolarization of the fiber membranes initiates a contractile process within these cellular elements It is possible to dissociate the electrical response from the mechanical to some degree but under normal circumstances the two are intimately linked It is, therefore, reasonable to *include in a consideration of cardiac excitability and the changes* occurring therein some discussion of the nature of mechanical activity in the heart The description of the cycle of events which is given here has been derived from that proposed by Wiggers (1928, 1953)

MECHANICAL EVENTS OF THE NORMAL HEART CYCLE

AURICULAR SYSTOLE AND DIASTOLE Each normal heart beat begins with the origin of the excitatory process in the pacemaker Propagation of this process evokes contraction of the auricles As the auricles complete their mechanical response and begin to relax, the ventricles start their contraction Auricular systole lasts approximately 0 11 second There is practically no intersystolic interval between auricular and ventricular contractions although there is an appreciable pause—the PR interval—between the recorded electrical responses of these chambers In further description of the mechanical events of the cardiac cycle little need be said about auricular systole and diastole save that *contraction* begins first near the pacemaker and follows in the wake of the action potential as it is propagated throughout the two auricular chambers

Those fibers initially excited begin to relax before others have attained their maximum degree of systolic shortening. The slight retardation of conduction which occurs at the A V node permits the onset of auricular relaxation before ventricular systole begins.

VENTRICULAR SYSTOLE Two definite phases are recognized during ventricular systole namely, isometric contraction and the ejection phase (Figure 78).

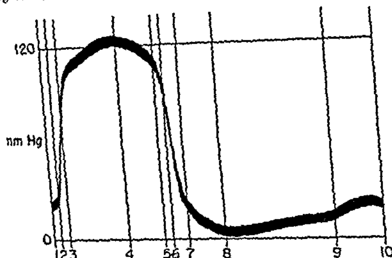


FIGURE 78. Phases of ventricular cycle 1 2, "entrant phase" 1-3 isometric contraction 3-5 ejection period showing minimum, maximum (4) and declining phases 5-6, protodiastole 6-7 isometric relaxation phase 7-8, phase of rapid ventricular filling 8-9 period of slow ventricular filling or diastasis 9-10 auricular systole

1 *Isometric contraction* When the ventricles start contracting the auriculo-ventricular valves close. At this moment the semilunar valves are also closed. It is not until the pressure within the ventricle has attained a value equivalent to that in the aorta or in the pulmonary artery that the semilunar valves open and blood flows into these large arterial trunks. The isometric contraction phase extends from the beginning of ventricular systole until the time of opening of the semilunar valves thus lasting for about 0 04 second. During this period all the valves are closed and no blood can either enter or leave the ventricle. Tension increases within the ventricle because of contraction of the muscle fibers but little change in shape or volume is possible.

2 *Ejection phase* When the semilunar valves open, blood is ejected from the ventricles into the aorta and the pulmonary artery, thus creating the arterial pulse During the initial moments of ejection the head of pressure responsible for volume flow of blood into the aorta or pulmonary artery is small, the ejection rate then gradually increases to a maximum and subsequently declines The total ejection phase lasts for about 0 25 second

VENTRICULAR DIASTOLE Four definite phases can be recognized during ventricular relaxation and the subsequent pause 1) protodiastole, 2) the phase of isometric relaxation, 3) the phase of rapid ventricular filling and 4) that of slow ventricular filling or diastasis

1 *Protodiastole* When, due to subsidence of contraction in the myo cardial elements, the ejection force created by ventricular systole begins to drop intraventricular pressure falls below that in the great vessels and the semilunar valves close This interval of change in the gradient of *intraventricular and arterial pressure which is abruptly ended by* the closure of the semilunar valves is the protodiastolic period In aortic pressure records it is clearly delimited by the aortic incisura and lasts for approximately 0 04 second in man and 0 02 second in the dog

2 *Isometric relaxation phase* The semilunar valves close at a moment when the auriculo ventricular valves have not yet opened again creating an interval during the cardiac cycle when blood can neither enter nor leave the ventricles Thus isometric relaxation takes place This phase lasts for about 0 09 second and is terminated by opening of the A V valves which occurs when intraventricular pressure falls below that main taining in the auricles

3 *Rapid ventricular filling* Once the A V valves open, a considerable proportion of the blood accumulated in the auricles during the period when *the valves were closed flows into the ventricles in a relatively short* time This quick inflow constitutes the phase of rapid ventricular filling which lasts for about 0 11 second in man and 0 06 second in dogs It is not clearly portrayed by intraventricular pressure records but is definitely shown by records of intra auricular pressure or ventricular volume It should be emphasized that ventricular filling during this phase of the cardiac cycle is entirely passive The rapid filling does not result immedi ately from any *contraction of cardiac tissue*

4 *Slow ventricular filling or diastasis* The rapid inflow of blood just

described does not complete ventricular filling Subsequently a more moderate and slowly declining inflow persists because a pressure gradient is maintained by the blood returning from the periphery of the body or from the lungs The slow decline of the inflow to the relaxed ventricles is due to a gradual build up of intraventricular pressure as they are distended The phase of low ventricular filling lasts until the auricular systole of the next cycle Consequently its duration is determined more than any other phase so far described by the duration of the heart cycle. If the heart rate is normal it lasts for about 0 19 and 0.29 second in man and dog respectively

ASYNCHRONOUS ACTIVATION OF MYOCARDIAL ELEMENTS

There is widespread evidence indicating that during normal contraction of the heart not all of the myocardial units attain the contracted condition simultaneously A certain time is required to activate the whole auricular or ventricular myocardium (Lewis and Rothschild 1915 Harris 1941) The activating process can be thought of as being a recruiting mechanism progressively and quickly incorporating more and more fibers into the contracted condition (Wiggers 1928) Therefore it can be assumed that not all of the myocardial fractions end their contraction at the same time. Presumably those that begin to contract first are also the first to relax. The total sequence of surface activation in the dog heart lasts for 18-23 msec It may be presumed that in man the total duration will be about twice that in the dog

Asynchronous myocardial activation is portrayed in the intraventricular pressure record by a relatively slow increase of pressure at the beginning of the isometric contraction phase This period has been called by Wiggers (1928) the "entrant phase" When all the fractions have been activated the record shows a steeper and much faster increase of pressure (Figure 78)

This recruitment of myocardial elements during activation has an important bearing on problems of irritability The processes of membrane depolarization and repolarization will not occur at precisely the same time in all fibers even if they lie in close proximity The complexities of the anatomical arrangement of the fibers contribute to make even more intricate the asymmetries of the activation-deactivation processes in any given portion of heart muscle During the recovery of excitability the heterogeneous conditions prevailing in neighboring fibers become of particular importance in determining the reactions to very strong stimuli.

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RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL EVENTS

The sequence of mechanical events just described results from the regular spread of excitation over the auricles across the specialized A V conducting system and throughout the ventricles It is of interest to examine the exact temporal relationship between this electrical activity and the contraction which it elicits. In the case of the intact heart the progressive recruitment of additional contractile elements makes such a study quite difficult. However in a small isolated fragment of the myocardium such as the papillary muscle wherein the conduction time is very short relative to the total duration of mechanical activity a reasonable comparison can be made between the time of depolarization and repolarization on one hand and contraction and relaxation on the other Such a comparison has been attempted in the case of isolated papillary muscle of the dog and cat ventricle

LATENCY In this work isometric tension was recorded by means of an electronic transducer (RCA #5734) and the onset of electrical activity by means of an intracellular microelectrode. The papillary muscle was stimulated at multiple points along its surface to eliminate as far as possible the effect of impulse propagation Records obtained from such a preparation (Figure 79 A) show that the latency between the onset of depolarization and the initial development of tension is less than 10 msec. It is likely, however that if it were possible to record contraction of only a small portion of a single fiber, even shorter values would be obtained since even in this preparation it is most likely that some conduction takes place and thus sequential activation of the contractile elements is still present.

REPOLARIZATION AND RELAXATION The relationships between depolarization and repolarization of the fiber membrane and contraction and relaxation of the papillary muscle during normal propagated activity are shown in Figure 79 B When electrical activity is recorded from the approximate center of the muscle it can be seen that the peak tension is reached simultaneously with the end of the plateau of the transmembrane action potential and repolarization precedes relaxation by only a short interval (since the total conduction time in this preparation is less than 10 msec., the distortion due to impulse propagation can displace the electrical record by only ± 5 msec) This approximate temporal coincidence of repolarization and relaxation suggests that the two phenomena

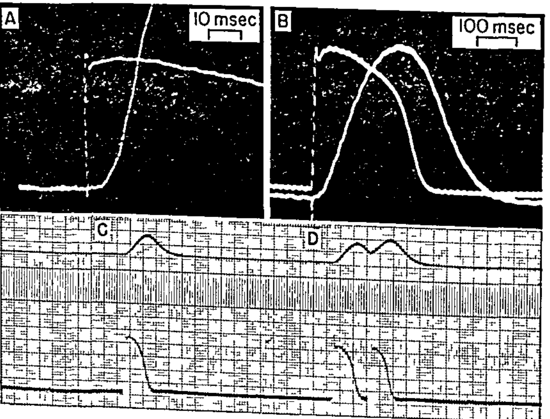


FIGURE 79 A—Transmembrane action potential and myogram recorded from a papillary muscle at a high sweep velocity showing latency between depolarization and onset of contraction B—Same at a slower sweep speed and less amplification of the myogram. (Retouched to show action potential upstrokes by dotted lines.) C—Records obtained from a papillary muscle poisoned with digitalis showing very short action potential duration and (D) the occurrence of summation of contractions with repetitive stimulation

may be causally related A similar relationship has been shown by others (Curtis 1949, Trautwein and Dudel 1954) On the other hand, records obtained under a variety of conditions, such as digitalis intoxication (Figure 79 C and D), show that repolarization is often completed long before the onset of relaxation A comparable disproportionate change in the duration of mechanical and electrical activity of the cat auricle is produced by acetylcholine (Burgen and Terroux 1953) Thus an immediate cause and effect relationship between the two phenomena is not invariably present. This matter will be discussed below in conjunction with the effects of heart rate on the duration of membrane activity and the onset of relaxation

EXCITABILITY AND CONTRACTION When mechanical activity of the intact ventricle is determined by recording the intraventricular pressure pulse and the electrocardiogram is simultaneously taken it is seen that the temporal relationship between electrical events and contraction is somewhat less consistent. A typical record given in Figure 80 shows that the earliest recorded development of tension usually follows the peak of the R wave and the T deflection is most often completed during protodiastole. If the excitability of the myocardium to test stimuli is studied simultaneously and related to the local electrogram and the intraventricular pressure pulse (Figure 80-A) absolute refractoriness is found to extend from the onset of electrical activity until the onset of relaxation and the recovery of excitability during the relative refractory period is completed long before the end of relaxation Thus the end of the irresponsive period precedes the completion of mechanical activity It is possible therefore to elicit a propagated action potential prior to the completion of relaxation Furthermore such a premature action potential does give rise to additional mechanical activity As seen in Figure 80-B this very early contraction most often manifests itself as a prolongation of the phase of relaxation although slightly later stimuli elicit a small increment in pressure before the trace has returned to the baseline In view of the adequate frequency response and small displacement of contemporary pressure transducers the distortion of such records by mechanical artefacts of this nature is unlikely It must be concluded therefore that a partial fusion of contractions of the normal mammalian ventricle can occur Other workers have supported this concept on the basis of a variety of studies (DiPalma and Mascatello 1951 Robb 1952 Whitehorn 1954) The occurrence of incomplete tetanus in the ventricular myocardium, under unusual conditions will be mentioned below

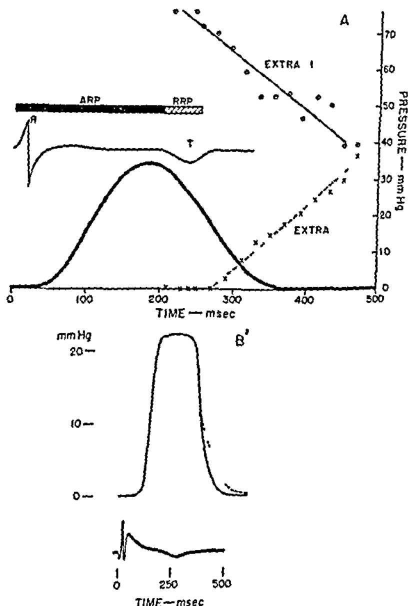


Figure 80 A Composite diagram showing the time relationship between a right ventricular pressure pulse and electrogram and the absolute (ARP) and relative (RRP) refractory period Also shown are the pressures developed by extrasystoles (x———x) and post extrasystolic beats (o——o) elicited during diastole and at various times in the relative refractory period

B Left ventricular pulse and electrogram showing the prolongation (———) of the pulse produced by an electrical extrasystole elicited during the T wave Dotted arrow shows time of extrasystole

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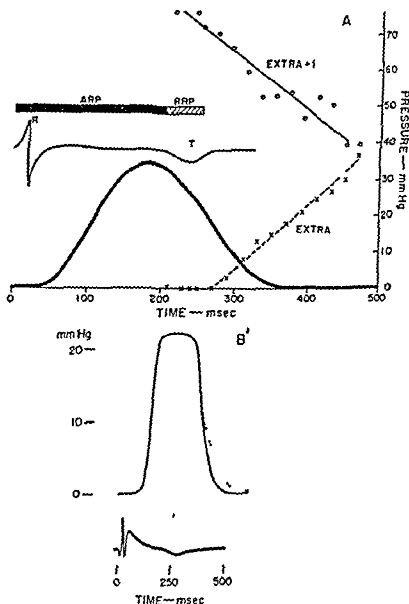


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B Left ventricular pulse and electrogram showing the prolongation (—·—·—) of the pulse produced by an electrical extrasystole elicited during the T wave Dotted arrow shows time of extrasystole

THE EFFECT OF CONTRACTILE FORCE ON EXCITABILITY It has been postulated that a change in the force of contraction may directly alter the excitability of the myocardium (Salter 1951) Recent work tends to disprove this contention In the case of the intact dog ventricle (Woske et al 1953) it has been shown that both a marked increase in systolic pressure resulting from partial aortic constriction and a decrease in pressure resulting from myocardial failure give rise to no demonstrable change in either resting excitability or the duration of refractoriness (Table 13) Similarly, Trautwein and Dudel (1954) found no change in either the magnitude or duration of the transmembrane action potentials of the cat papillary muscle during marked alterations in initial length and tension unless over stretching and irreversible damage to the muscle was produced It has also been observed (Woske et al., 1953) that in acute heart failure produced by ligation of the aorta in the dog ouabain (0 17 mg total dose) may have a marked therapeutic effect, restoring the strength of contraction to normal, without changing excitability No significant changes in thresholds to stimulation conduction times refractory periods nor the ability to respond to high driving rates are found in either the auricle or ventricle during periods of maximum force of contraction shortly after ligation of the aorta, during failure or after the force of contraction has been restored to normal by administration of ouabain It would seem that in the therapeutic range the glycoside effect is not concerned with excitability nor the duration of refractoriness in the failing myocardium but rather with energy utilization during systole proper Work of Wollenberger (1947, 1949) Bing et al. (1949 1950) likewise indicates that the failing heart does not properly use the energy available for contraction and that the digitalis glycosides can affect these processes and thus the mechanical responses of cardiac muscle without producing changes in excitability This does not imply that excessive dosage fails to influence both excitability and electrical activity (Coraboeuf et al. 1953 Stutz et al. 1954)

DISSOCIATION OF ELECTRICAL AND MECHANICAL EVENTS The possibility of achieving a complete dissociation between mechanical and electrical activity has been studied repeatedly (Garb 1951 a Wiggers 1953) In most instances it has been possible to show either that excitability and contractility can vary independently or that propagated electrical activity is still obtainable at a time or under conditions when there is no longer any recorded mechanical response In most cases it is

Table 13—Range of changes in diastolic thresholds absolute refractory periods total refractory periods and conduction times of ten animals and average change for the series Values are in terms of change in msec or ma. from control * *indicates values smaller than could be measured i e., less than 0 01 ma. or 2 msec An example of typical values obtained in one experiment is given*

		Diastolic threshold ma.		Absolute refractory period msec		Total refractory period msec		Conduction time between two points on muscle msec		Systolic B P average
Variation		Auricle	Ventricle	Auricle	Ventricle	Auricle	Ventricle	Auricle	Ventricle	
Typical values		0 37	0.36	90	135	130	185	15	10	100-120
Control	Range	0 to +0 04	0 to +0 16	−20 to +20	−10 to +20	−20 to +10	−20 to +10	0 to +10	0 to 0	
	Average	+0 01	+0 05	*	+6	*	+4	+3	0	
After Aortic Occlusion	Range	−0 03 to 0	0 to +0 05	0 to +20	0 to +20	0 to +40	0 to +20	0 to +10	−10 to 0	230-250
	Average	*	*	+10	+6	+13	+5	*	−2	
Failure	Range	−0 04 to +0 02	−0 06 to +0 03	−5 to +40	−5 to +20	−5 to +10	−5 to +30	−5 to +10	−20 to +20	30-50
	Average	*	*	+5	+8	+5	+11	0	−2	
Ouabain	Range	−0 06 to +0 05	−0 15 to +0 17	−30 to +25	−10 to +15	−15 to +30	−20 to +20	0 to +5	−5 to +20	200-230
	Average	0	*	+4	−2	+13	+2	*	+4	

difficult to decide whether contraction has actually been abolished or whether the tension developed is merely less than that which the transducer employed can record In either instance however, it is not surprising that at certain times the membrane phenomena associated with propagated excitation can be uncoupled from the usual contractile response, in view of both the complexity of the coupling process and the many factors which are known to influence the contractile proteins responsible for the development of tension

FACTORS INFLUENCING MECHANICAL ACTIVITY

For many years the major factors controlling the mechanical activity of the heart have been well documented These can be subdivided into intrinsic and extrinsic factors In the former category the most important are the initial or resting length of the fiber and the less well understood metabolic processes responsible for supply and utilization of energy Heart rate and the state of recovery of the myocardium are also determinants of the tension developed during systole In the second category fall such variables as the ionic composition of the extracellular fluids the presence of various autonomic mediators and changes in body temperature Certain a pects of several of these controlling factors have been studied in some detail in recent years and will be discussed more fully than others in the succeeding sections

LENGTH TENSION RELATIONSHIPS The length tension relationship of the isolated papillary muscle is similar to that found in other striated muscle Although the determination of "resting length" is somewhat uncertain if the papillary muscle is subjected to progressive increments of length, the tension developed during an isometric contraction increases up to a maximum and then falls off slowly as additional stretch is produced (Figure 81 A) This effect of initial (or diastolic) length on systolic tension was first studied in detail by Frank (1895) employing the isolated frog ventricle and later determined in the isolated mammalian heart by Starling (1915) Although there has been some disagreement as to whether initial length or initial tension is the major determinant (Katz 1935), there is no longer any doubt that it is the resting fiber length which is directly related to the systolic tension developed during activity The applicability of this relationship in toto to the intact, in situ heart is less certain The presence of a relatively indistensible pericardium limits the degree to which the ventricle can be stretched by

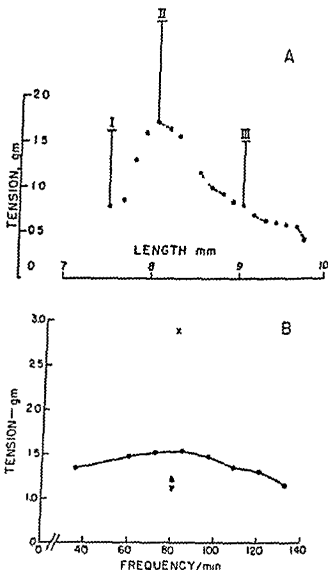


FIGURE 81 A Contractile tension developed in a driven papillary muscle at different initial lengths (•———•) I II and III show maximum tension increment produced by an extrasystole at lengths less than equal to and greater than optimum

B The effect of rate on systolic tension in a driven papillary muscle (•—•) In another muscle maximum tension developed when driven at 80 per min (▲) with regularly spaced stimuli tension developed when driven at a basic rate of 40 per min with every driven beat *followed by a stimulus producing an early extrasystole* (X) Return to original rate of 80 per min (▼)

increments in filling pressure. Because of this, it is most likely that the normal heart never attains a length at which the systolic tension is decreased (Sarnoff 1955 Rushmer, 1955) In chronic heart disea e, on the other hand with marked cardiac enlargement, it is quite possible that over-distension of the ventricle and a consequent decrease in systolic force may occur The dramatic effect of measures which decrease central venous pressure in congestive failure strongly suggest that over-distension in this particular case is of paramount importance.

Although the mammalian auricle has been studied less frequently than the ventricle with respect to this property, it has been shown that initial fiber length has an effect similar to that obtained in the case of ventricular myocardium (Little et al. 1953)

HEART RATE The effect of frequency of contraction on the systolic tension developed by cardiac muscle is rather complex The most detailed studies have been made with isolated hearts or fragments of isolated hearts since in this type of preparation the elimination of variables other than rate is more easily accomplished. On the other hand as will be discussed later many of the effects of rate clearly demonstrated by isolated muscle preparations are not prominent aspects of the function of in situ hearts

The staircase" phenomenon or treppe described by Bowditch (1871) is frequently found in isolated amphibian and mammalian hearts After a prolonged period of quiescence when regular contractions are resumed the tension developed by each systole increases progressively to a certain maximum. If the rate of contraction is then increased the systolic tension is again augmented (Figure 81 B) This increase of tension with increased rate continues until at very *fast rates* the tension falls and relaxation from each contraction becomes incomplete. Thus resting tension increases at the same time as the systolic increment falls off

When the transmembrane action potentials are recorded simultaneously with the isometric contraction and heart rate is increased progressively, it can be seen that there is an almost parallel shortening of the duration of both the action potential and the muscle twitch both the rate of rise and rate of fall of tension being increased at higher frequencies (Figure 82 A) As has been stated previously there is little decrease in the magnitude of either the action potential or resting potential until excessive rates are attained.

The heart rate at which the maximum tension is developed varies greatly

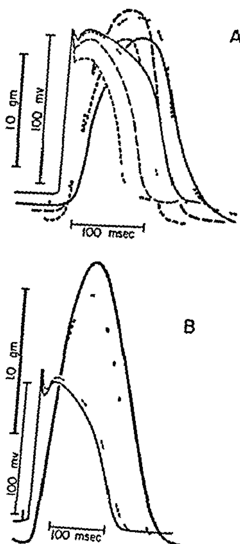


FIGURE 82 A Tracings of simultaneously recorded action potentials and myograms showing the configuration and amplitude changes recorded at heart rates of 30 (   ) 60 (— — —) 120 (   ) and 180 (——) beats per minute

B Tracings as in A showing the first two contractions following a prolonged rest First beat (——) second beat (   )

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in different muscles and also in a single muscle when other factors are changed Typically, however, treppe is least marked immediately after isolation of the preparation Also, as fatigue progresses, the contraction frequency required for optimum tension is elevated. On the other hand, in the case of the intact mammalian heart, if other conditions are unchanging alterations in heart rate have little effect on systolic tension

Hajdu (1953) and Szent Györgyi (1953) have explained the 'treppe' phenomena on the basis of an increased loss of both potassium and water from the intracellular space during activity This net loss of potassium increases the tendency for association of actomyosin and thus augments the twitch tension Similarly, the excessive loss at high rates results in contracture and consequent loss of systolic increment in tension Hajdu also postulates that the magnitude of the resting transmembrane potential exerts an effect which favors the dissociation of actomyosin, probably by maintaining a low intracellular pH Thus a decrease in resting potential is associated with incomplete relaxation and the development of contracture

There are certain complexities in the relationship between frequency of contraction and systolic tension which are not easily explained on the basis of the theory mentioned above Foremost among these is the so called "rest contraction" (Rosin and Farah, 1955) If an isolated papillary muscle (Cattell and Gold, 1941 a) or auricle (Rosin and Farah, 1955) is stimulated at a regular rate and then stimulation is suddenly stopped for a brief interval the first contraction on resumption of activity is greatly increased in magnitude (Figure 82 B) Since the only transfer of K likely to occur during the brief rest is an increase of intracellular potassium, the augmented tension of the first beats following the rest suggests a contradiction to the theory proposed Similarly, the potentiation of the initial contraction persists even when the period of quiescence is prolonged up to several minutes, an interval long enough for potassium and water to return to resting quantities inside the fiber Only after rest periods of considerably longer duration is the tension of the initial beat decreased and the treppe phenomenon again manifest

On the other hand, a large amount of experimental evidence supports the concept that changes in the potassium content of the fiber are intimately related to the tension developed during contraction The positive inotropic effect of digitalis glycosides adrenaline adrenal steroids low temperature and low extracellular potassium are all associated with an increase in

the net outward flux of K^+ during activity (Hajdu 1953) Similarly the decrease in tension resulting from barbiturates procaine cocaine, chlore tone and physostigmine is accompanied by a decrease in potassium efflux (Holland 1954) Thus although there are still many a pects of the problem which have not yet been resolved the essential role of the intra cellular ionic content in regulating the tendency for actin and myosin to associate is beyond doubt To what extent this regulatory factor is operative in determining the changes in systolic tension encountered during normal cardiac activity remains uncertain

THE EFFECT OF IONS Changes in the ionic composition of the extracellular fluid have a profound effect on the tension developed during systole Although there are certain differences between species and between auricle and ventricle of the same animal the major action of certain ions can be ummarized rather briefly

A decrease in the concentration of extracellular sodium is associated with an increase in the contractile force of the muscle (Clark, 1912) Such a change in sodium concentration apparently acts by means of the loss of Na and water from the fiber which occurs (Hajdu 1953) and not as a result of alterations in the intracellular *concentration* of this ion The latter possibility is ruled out by the ob ervation that large changes in concentration of intracellular electrolytes resulting from variation in the glucose content of the extracellular fluid have little or no effect on the force of contraction Thus as in the case of treppe the total fiber content of Na or K appears to be most important with respect to the development of tension rather than their concentrations

The effects of potassium are perhaps more marked than those resulting from alteration in Na however as in the case of electrical activity it is difficult to differentiate between changes directly related to an alteration in K and those resulting from a change in the ratio of K to Ca^{++} As can be seen in Figure 83 low extracellular potassium greatly augments the isometric tension of the isolated papillary muscle at all rates of activity, and elevated K has the opposite effect. On the other hand if the Ca^{++} concentration is decreased in proportion to the change in K the tension is lowered to or below control values while an increase in Ca^{++} with K constant gives as great an increase in tension as that produced by low potassium Hajdu (1953) has po tulated that the changes in tension following alteration in extracellular K concentration are the result of a net change in fiber K and water Whether the actions of Ca^{++} are

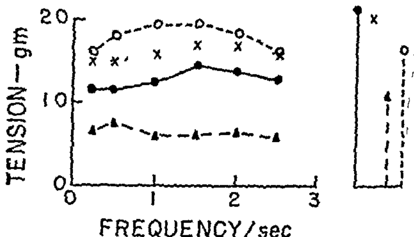


FIGURE 83 Records obtained from an isolated papillary muscle showing the effect of changes in the ionic composition of Tyrode's solution on the relationship between frequency of contraction and systolic tension (on the left) and on the maximum post extrasystolic potentiation of contraction (on the right) Control (Ca=2 7 K=2 7 mM) •—• , low potassium (Ca=2 7, K=0 65 mM) x——x, low potassium and calcium (K=0 65 Ca=0 65 mM) Δ——Δ and high calcium (Ca=10.8 K=2 7 mM) o——o

brought about by changing the permeability of the membrane to potassium, or by some other means is not certain However the demonstration that Ca^{++} in proper concentration augments the tension developed by isolated actomyosin filaments (Edman, 1953) suggests that this ion may act directly on the contractile mechanism

Many other ions have been found to influence the contractility of cardiac muscle The complete lack of Mg^{++} has little effect on the papillary muscle of the cat, as does a high concentration of this same ion (Garb 1951 b) On the other hand, in the case of the guinea pig auricle (Holland, 1953) Mg^{++} excess produces a profound depression of the contraction Strontium, in the presence of a normal Ca^{++} concentration, increases the contractile force but when the Ca^{++} level is low added Sr^{++} gives rise to a decrease in systolic tension (Garb, 1951 b) NH_4^+ has been shown to increase the tension developed during contraction, while Ba^{++} increases the systolic tension and antagonizes the action of excess K^+ However with respect to ionic imbalances which are encountered in man, the effects of Na^+, K^+ and Ca^{++} are not only most important but also most nearly understood in terms of mode of action

DIGITALIS GLYCOSIDES Because of the great therapeutic importance

of digitalis this substance has been studied frequently in both intact and isolated preparations (Cattell and Gold, 1938 1941 b, Gold and Cattell, 1940, Woske et al 1953 Levine et al. 1951) Some additional information concerning the manner in which it influences contractility of cardiac muscle has been provided by recent investigation Early work demonstrated that this agent has little effect on the contractility of the normal myocardium only when the contractile force is diminished does digitalis exert a positive inotropic action The investigations of Szent Gyorgyi (1953) and Hajdu (1953) provide a reasonable explanation for these findings The contractile force of the myocardium according to their work, depends upon the total quantity of Na and K within the fiber Also, substances normally present in the serum maintain the level of (Na plus K) near the optimum Under these conditions additional loss of electrolyte and water under the influence of digitalis, will result in contracture and a decrease in systolic tension On the other hand, when the condition of the myocardium is outside this optimal range, the loss of potassium resulting from digitalis administration will increase the tension developed during contraction. The demonstration (Stutz et al., 1954) that digitalis fails to influence the tension of glycerin-extracted heart muscle wherein membrane activity is absent, supports the concept that the action of this compound is somehow related to changes produced in membrane permeability On the other hand it has been shown that excess K will reverse the toxic actions of digitalis but fails to decrease the positive inotropic effect of this agent (Garb and Venturi 1954) It cannot be stated with certainty moreover that no other effects occur Other workers have shown that digitalis glycosides increase contraction of actomyosin filaments in the presence of certain Ca^{++} concentrations and seems to have some effect on the ability of the myocardium to utilize available phosphate bond energy (Rothlin et al., 1955) The possibility remains therefore that the mode of action is more complex than that suggested above.

Many studies have described marked changes in cardiac excitability resulting from the administration of digitalis (Wedd et al 1941) Recently, this agent has been shown to produce changes in the transmembrane potentials of isolated mammalian and amphibian hearts consisting of a decrease in the resting and action potential amplitude and a shortened action potential duration (Coraboeuf et al., 1953 Stutz et al., 1954) There is some question, however whether similar changes result from

therapeutic concentrations of this agent In the case of the in situ dog ventricle (Woske et al, 1953) it has been demonstrated that concentrations of digitalis adequate to completely restore maximal systolic force during induced myocardial failure give rise to no change in either the level of resting excitability or the time course of the recovery of excitability following activity

EXTRASYSTOLES AND POST EXTRASYSTOLIC POTENTIATION

McWilliam (1888) first reported the observation that a single extra systole results in an increased systolic tension of the succeeding contractions Subsequently Cattell and Gold (1941 a) studied this phenomenon in the isolated papillary muscle of the cat heart They noticed that the degree of potentiation is directly related to the prematurity of the extrasystole and that the effect has a long duration many beats following the extra systole being augmented in amplitude Moreover, the amount of potentiation is increased by the presence of repeated extrasystoles A marked similarity between this effect of an extrasystole and the 'rest contraction" discussed earlier is apparent

A similar phenomenon is also observed when intraventricular pressure is recorded from the intact mammalian ventricle and either spontaneous or induced extrasystoles occur The tension of the extrasystole is less than that of the normal contraction and the systolic tension of the succeeding normal contraction is greatly augmented The usual explanation for the low tension of the extrasystole is that because of its prematurity filling has been inadequate and the diminished initial length results in a weaker contraction (Wiggers 1925) Similarly, the additional tension of the next beat, which usually follows a compensatory pause is said to result from increased filling greater initial length, and thus greater systolic force This explanation is in keeping with the relationship clearly formulated by Starling (1915) and discussed earlier in this chapter

Because of the similarity between the phenomenon seen in both the isolated papillary muscle, at constant initial length, and the intact heart it is of considerable interest to re evaluate the role of changes in filling in the production of the changes in systolic tension just described This has been accomplished by comparing the effect of extrasystoles on intraventricular pressure in normal hearts where changes in both filling and ejection were possible with results obtained after the right ventricle had been bypassed by a pump (Siebens et al, 1956) In this latter case,

the entire venous return to the right heart was directed into a large reservoir so that the filling pressure of the right ventricle could be controlled. In addition the pulmonary artery was ligated to prevent ejection for this reason contractions were nearly isometric throughout and emptying of the ventricle during systole was not possible. Intraventricular pressure was recorded from the right and left ventricle by means of capacitance manometers and indwelling catheters or short cannulae. Changes in diastolic volume were induced by injecting or withdrawing known volumes of blood from the right ventricle In most cases both the cardiac output and systemic blood pressure could be maintained within normal limits after isolation of the right ventricle. In some experiments dilatation of the right ventricle resulted in incompetence of the tricuspid valve results obtained under these conditions were not valid and were discarded from consideration

The results obtained in this series of experiments can be described as follows (Siebens et al. 1956) Pressure pulses recorded from the *isolated* right ventricle showed similar changes following an extrasystole to those obtained from the same ventricle prior to isolation (Figure 84-B) The tension of the extrasystole was decreased and the tension of the beat following the extrasystole was greatly increased In addition the potentiation of the post-extrasystolic beat was *greater* in the absence of filling than in the normal heart As in the case of the isolated papillary muscle the earlier the extrasystole the less tension *it developed* and the greater the tension of the following contraction Moreover the augmented tension resulting from a single premature contraction declined slowly over a period of several beats. The possible role of an altered diastolic interval was evaluated in several ways In the first place, it was noted that a measurable mechanical response was not present following extrasystoles induced early in the relative refractory period the only change in the pressure pulse was a slight prolongation of the descending limb of the previous normal contraction. However even though there was no mechanical response capable of altering filling in the intact heart, these early extrasystoles were most effective in augmenting the tension of the next beat. In addition the effect of a single dropped beat was compared with that of the mechanically ineffective extrasystole in both the intact heart and isolated right ventricle (Figure 84-A) Again the potentiation resulting from the extrasystole was much greater than that produced by the dropped beat even though the compensatory pause was longer in the

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latter instance These results strongly suggest that the potentiation of beats following an extrasystole is a direct result of the extrasystole and is not related to any change in filling or initial fiber length

Several additional observations tend to confirm this impression When the filling pressure, and thus diastolic size of the isolated right ventricle was elevated by known increments the tension of the normal driven beats the extrasystole and the post-extrasystolic contraction were all increased However the effect of increased initial length was much less in the case of the extrasystole and much more in the case of the post-extrasystolic beat than the effect of the same change in initial length on normal driven beats. This suggests that not only is the potentiation of the beat following an extrasystole not due to added filling but also that the weak contraction of the early extrasystole is a result of the prematurity of the contraction and is not due to any decrease in filling or fiber length It is apparent from this latter observation that recovery of ability to contract is much slower than recovery of normal excitability at any diastolic tension or length.

The results of these studies strongly support the concept that the changes in systolic tension of early extrasystoles and also the increase in systolic tension of the post-extrasystolic beats are produced by the early propagated electrical response and are not related to any change in ventricular filling or *initial fiber* length However, since in the experiments described the possibility remained that some minor alteration in fiber length *might* have gone unnoticed similar studies were conducted with isolated papillary muscles. In these experiments isometric tension was recorded directly with a sensitive electronic transducer and changes in tension could be directly observed The results of this work are reported in detail elsewhere (Hoffman et al. 1956) However several observations are pertinent at this time.

The role of initial length or tension in the production of post-extrasystolic potentiation was evaluated by studying the effect of extrasystoles at three different initial lengths namely, at lengths less than, equal to and greater than optimum. In the first case an increase in resting length or tension would increase the amplitude of contraction in the third case on the other hand, a decrease in twitch amplitude would be the result of the same change in length As can be seen in Figure 81 A at all three initial lengths the early extrasystole had the usual effect on systolic tension, the contractile force being greatly augmented It is apparent, therefore

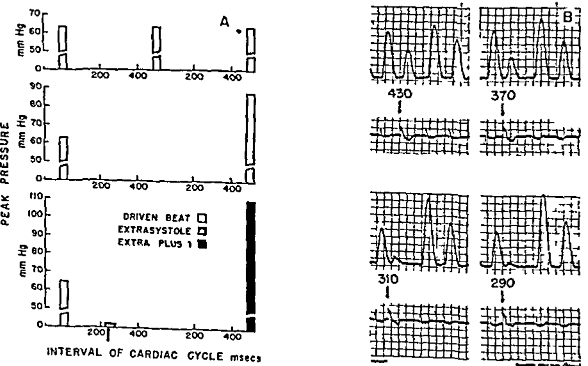


FIGURE 84 A The relationship between diastolic interval and systolic tension of the isolated right ventricle showing three succes ive normal beats (top) a single dropped beat and the subsequent increased systolic tension (middle) and the interposition of a mechanically ineffective extra systole which produces a greater increment in systolic ten sion of the subsequent beat (bottom)

B Ventricular pressure pulses and electrograms recorded from the isolated right ventricle showing the effect of ex trasystoles induced at the intervals shown (in msec.) on the figure

that the effect of extrasystoles is not mediated through changes in the pre-systolic length or tension of the fiber The possible role of heart rate could also be evaluated in this preparation in the following manner The papillary muscle was driven at a wide range of rates to establish the optimum frequency of contraction for the development of tension Subsequently the tension developed at this rate during normal driving stimulation was compared with that resulting from the application of the same number of stimuli per second, but with every other stimulus close enough to the preceding shock to cause only a premature contraction As shown in Figure 81 B the systolic tension during the production of repeated extrasystoles was greater than that resulting from any frequency of regularly applied driving pulses. The role of frequency of contraction therefore, is of minor importance in the production of the post-extrasystolic potentiation

It was of interest to record the transmembrane potentials during the production of post-extrasystolic potentiation since it has been postulated that an increase in the duration of depolarization is associated with an augmented force of contraction Representative records obtained from the papillary muscle are shown in Figure 85 A. The great increase in contractile force following repeated extrasystoles was associated with a minor decrease in the duration of the action potential and no change in either the resting potential or the amplitude of the action potential A similar decrease in duration is seen during accelerated heart rate (Figure 82 A) on the other hand the augmented tension of the "rest contraction" is accompanied by a slight increase in action potential duration (82 B) It is thus not possible to ascribe the increase in contraction to a change in the duration of depolarization of the fiber membrane.

It was also observed that there was no apparent change in conduction velocity of the potentiated contraction. In addition when a series of beats was recorded on the same time base, it was apparent there was no change in the time of maximum tension development and only a slight increase in the over all duration of the contraction (Figure 85 B) Thus a more rapid recruitment of the various fibers during contraction or an increased duration of contraction in each element seem to be of little importance in the development of increased tension following single or multiple extrasystoles

The effect of cooling, of changes in the ionic composition of the extracellular fluid and of agents with a positive inotropic action (digitalis

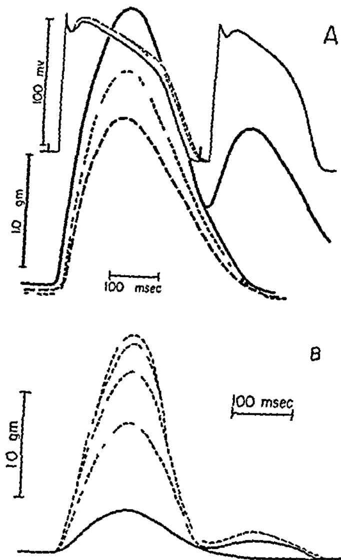


FIGURE 85 *A* Simultaneous tracings of the transmembrane action potential and myogram of the isolated cat papillary muscle showing the effect of an extrasystole on both records Controls (— — —) post-extraystolic potentiation (----) return towards normal ( )

B Superimposed tracings of a myogram recorded from a dog's papillary muscle showing the control tension (——) and the tension changes during repeated premature contractions (— — —)

addition, epinephrine has been reported to abolish the ability of the mammalian heart muscle to summate at the same time as it shortens the duration of refractoriness (Whitehorn 1954) In view of these apparent discrepancies some re-evaluation of the question of summation and incomplete tetanus in mammalian heart muscle seems indicated

It has been demonstrated (Figure 79) in the isolated papillary muscle that relaxation normally follows soon after repolarization Furthermore, soon after any one contraction the myocardium is capable of developing little tension if stimulated again However, in records obtained from both intact hearts (Figure 80) and isolated muscles (Figure 82) an incom plete fusion of an early extrasystole with the preceding contraction is often evident. Even under normal conditions, therefore, something akin to incomplete tetanus can occur On the other hand the production of frank summation and incomplete tetanus results whenever there is a dis-proportionate change in the length of electrical and mechanical activity Thus digitalis in high doses which result in a very short action potential and completion of repolarization long before relaxation, produces incom plete tetanus in heart muscle exposed to rapid stimuli (Figure 79 C and D) Epinephrine, on the other hand, not only decreases the duration of the refractory period but also increases the rate of relaxation (Opdyke 1952) in this case summation is prevented even in the presence of a decreased irresponsive period

These observations in addition to others mentioned previously, suggest that although *repolarization* of the membrane influences both the time of relaxation in the myocardium and also the time of restoration of full contractility repolarization is separable in time sequence from relaxation Moreover recovery of normal excitability and contractility and relaxation outlasts repolarization When this occurs there is an increased probability of abnormal responses and incomplete fusion of mechanical activity

SUMMARY

This chapter includes a brief description of the mechanical events of the cardiac cycle and the asynchrony of activity of myocardial elements

The mechanical activity of cardiac tissues is evoked by the propagated action potential and occurs with a brief latency after depolarization of the membrane. A relationship exists between depolarization and repolarization of fiber membrane on the one hand and contraction and relaxation on the other, but these processes are somewhat separable in that repolarization

epinephrine) were also studied (Hoffman et al, 1956) In no case was there a consistent abolition of the potentiating effect of extrasystoles, although the augmentation produced was less when the contractile force was initially high due to any of these agents Finally, it was noted in the papillary muscle, as in the case of the intact heart, that stimuli applied so early in the refractory period as to be ineffective in eliciting a propagated action potential had no effect on the tension of the following contractions

The results of these studies lead to certain conclusion although the nature of the potentiation produced by extrasystoles remains uncertain In the first place, the role of changes in initial length or tension, in both the intact and isolated preparations, is of much less importance in producing post-extrasystolic potentiation than has been assumed on the basis of the well known Starling law Furthermore, the potentiation thus produced is not due simply to the change in heart rate The fact that early extrasystoles develop less tension than normal, even when the ventricle is optimally filled, shows that the recovery of the contractile mechanism is much slower than the recovery of excitability Moreover, since mechanically ineffective extrasystoles are still capable of augmenting the force of the following contraction, it appears that it is the propagated action potential which brings about the potentiation of contractions following extrasystoles The immediate development of this potentiation and its long duration are difficult to reconcile with the theory (Hajdu, 1953) that potassium loss is the major determinant of the force of systolic contraction An alternative hypothesis in better agreement with the experimental observations, however, is difficult to formulate at this time

SUMMATION OF CONTRACTION AND TETANUS IN MAMMALIAN CARDIAC MUSCLE

The statement is commonly encountered that summation of contraction does not occur in cardiac muscle because of the long duration of the refractory period, or more correctly the irresponsive period. Moreover numerous experiments have demonstrated that under a variety of conditions summation can be produced when the refractory period is shortened (Carlson 1906, Burridge, 1920, DiPalma and Mascatello 1951 Whitehorn, 1954) On the other hand, cooling of the mammalian heart regularly results in the production of summation and incomplete tetanus during rapid stimulation even though the decrease in temperature causes a marked prolongation of refractoriness (Trautwein and Dudel, 1954) In

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may be completed before the onset of relaxation The temporal relationship between electrical events and contraction is not absolutely fixed

Cardiac excitability is likewise not invariably linked in a quantitative fashion with the force of contraction of the myocardium The strength of beat may change and digitalis and other agents may modify the efficiency of energy use in cardiac contraction without change in transmembrane resting and action potentials or in excitability as determined by applied stimuli

Factors influencing mechanical activity are discussed Tension heart rate, changes in concentration of ions, temperature, digitalis and other factors all influence the contractile process in cardiac muscle Evidence is offered both in support of and opposed to the concept that changes in the potassium content of the fiber are intimately related to the tension developed during contraction

Much of the newer experimental work reported deals with a study of treppe like phenomena The long lasting potentiation of contraction following early extrasystoles was studied in the whole heart in situ and in isolated tissues It appears that though the transmembrane action potentials are not changed, the propagated membrane changes, even though unaccompanied by contraction, somehow affect the contractile processes during subsequent cycles

The relation of this post extrasystolic potentiation to phenomena usually explained on the basis of Starling s Law of the Heart is pointed out

Summation of contraction in cardiac muscle is discussed and possible explanation of the unusual conditions responsible for its occurrence is given

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of specialization since beats normally originate in a pacemaker such as the sinus venosus of amphibia and reptiles and the nodal tissues of mammals

Neurogenic hearts are driven by cholinergic neurons and consequently they are accelerated by acetylcholine Activities of the myogenic hearts are controlled rather than initiated by neural factors They are normally maintained in an intermediate state of activity by tonic discharges from opposed autonomic nerves Since the inhibitory nerves are cholinergic acetylcholine generally inhibits or slows the rhythmic action of the mammalian heart. The electrocardiograms from neurogenic hearts usually show traces of the burst of ganglionic impulses that originate the beats These may appear as oscillations on the cardiographic tracings (Prosser, 1950)

Myogenic hearts of various species differ from each other in many respects For example the pulse rates range from a few beats per minute in the case of some shellfish to several hundred beats per minute in small warm blooded birds and mammals Clark (1927) gives many examples of the diversity of heart rates encountered in the various species Even within the mammalian group there are large diversities Figure 86 gives a comparison of the electrocardiograms and the cellular transmembrane action potentials of a number of forms The electrocardiograms of other animals can be found in publications by Fiddes (1929) Prosser (1950) Lombard (1952) and White (1953) The similarity of the electrocardiogram of the eel (Arvanitaki and Cardot, 1936) to an electrical recording from smooth muscle of the uterus (Bozler, 1942) and the electrocardiogram of the mouse to the action potential of skeletal muscle emphasizes the similarities of cardiac and other types of muscle.

VARIABILITY OF CHARACTERISTICS These diversities of property and action are exaggerated by various circumstances In true hibernation the heart rate may drop to a very few beats per minute and during stress and excitement the rate may rise to above 200 per minute in the same individual The configuration of the electrocardiogram and the duration of even the transmembrane action potentials of individual cells change enormously as the heart rate varies At extreme rates, as in fibrillation these potentials begin to resemble the action potentials of skeletal muscle and under certain conditions e g extreme cold the repolarization is slowed and the cellular action potentials show more resemblance to those of smooth muscle (see Chapters V VII VIII)

XII Comparative Physiology of the Heart and Summary and Conclusions

A consideration of comparative cardiac physiology and a brief summary of the points of major importance treated in this monograph are given

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THESE STUDIES of the mammalian heart as a whole and of the function of its individual elements have led to numerous conclusions and have revealed several phenomena of great interest In addition they have served to indicate many problems which appear to be eminently worthy of continued investigation In brief summary the main themes and conclusions of the monograph can be reviewed under a number of headings

SPECIAL PROPERTIES OF HEART TISSUES

All species of animals except members of the phyla protozoa porifera and echinodermata possess a muscular circulatory pumping organ which can be called a heart In their phylogenetic and ontogenetic development these hearts originate from smooth and/or skeletal muscle and heart muscle does appear to possess some characteristics of both In addition however, the heart tissues have developed properties which adapt these organs to meet peculiar functional requirements of the various species (Clark, 1927) These special properties of heart tissues are most highly developed in the large mammalian hearts which may be considered to be the most specialized of all such organs A consideration of the comparative physiology of the heart is of interest because such studies provide examples of specializations which emphasize the functional importance of certain properties acquired by heart tissues

TYPES OF HEART Two basic types of heart exist the neurogenic and the myogenic Neurogenic hearts are characteristic of the phylum arthropoda and possibly some ascidia while mollusca and vertebrata possess myogenic hearts In neurogenic hearts, beats originate in ganglia located on the heart surface (Heinbecker and Bishop 1935 Carlson and Johnson, 1953) while in myogenic hearts the rhythmicity seems to be a property of the heart muscle itself In this latter group there is some degree

Similarities and dissimilarities of the hearts of various species and of specialized heart tissues can be given further consideration in connection with a discussion of the conclusions attained in this total study of the phenomena of heart action The topics of major interest which have been dealt with are the following

EXCITABILITY AND EXCITATION

It can be stated that current theories concerning the nature of the excitatory processes and conduction are applicable to the heart cell as well as to nerve fibers There appears to be a basic similarity between membranes of all irritable cells Excitation and conduction are membrane phenomena and aside from quantitative differences in threshold and membrane potential the nerve, skeletal muscle and heart muscle cell resemble each other very closely

The cardiac cell membrane has a structure and composition which confer a partial permeability and a polarization of the membrane by virtue of intrinsic chemicophysical processes Metabolic activity sustains this normal state despite intrinsic and extrinsic influences which must be counteracted This functionally balanced state provides opportunity for creation of an instability of the heart cell such that impinging influences

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FIGURE 86 Electrograms, electrocardiograms and transmembrane action potentials of various animals

(A) Upper Dog limb lead ECG Lower Ventricular transmembrane action potential recorded simultaneously

(B) Upper Electrogram from dog auricle Lower Simultaneous transmembrane action potential

(C) Upper Transmembrane action potential of frog ventricle Lower Electrogram from frog ventricle

(D) Transmembrane action potential of excised canary ventricle

(E) Transmembrane action potential of excised goldfish ventricle

(F) Upper Electrogram of rat ventricle. Lower Transmembrane action potential of rat ventricle.

(G) Electrocardiogram of pigeon. (Reproduced from Lewis, 1913)

(H) Electrocardiogram of goldfish. (Reproduced from Lewis, 1913)

(I) Transmembrane action potential of rat ventricle

Transmembrane action potentials are 60-90 mv Electrograms and electrocardiograms are a few millivolts. Time marks in D and I are 10 and 50 msec. Dots in E are 50 msec. In G and H time marks are 200 msec. (Retouched to show action potential upstrokes by dotted lines.)

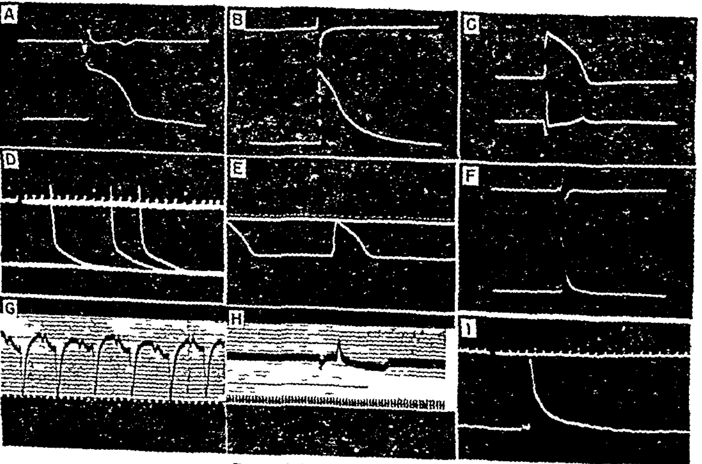


Figure 86 (*See legend facing page*)

intrinsic excitatory processes and because excitation abolishes any development of an excitatory process which may have begun.

The sinus venosus of the amphibia and reptiles and in the mammals the sino-auricular node serve as the pacemakers There is a graded order of intrinsic rhythmicities in the mammalian heart and this is sufficiently uniform to permit prediction of beat origin following destruction of the primary (the S A node) and even the secondary (A V node) pacemakers Ectopic beats however, can originate from any portion of the heart since cardiac muscle is comprised of an association of potentially autonomous elements and escape from domination by the normal pacemaker is always a latent possibility The spontaneous origin of a beat is always identifiable in a cell by the gradual decline of transmembrane potential which precedes the propagated response.

THE RECOVERY PROCESS

Following excitation of cardiac muscle and the propagation of an impulse the membrane is repolarized and other recovery processes occur In this respect, however heart tissues differ somewhat from nerve and skeletal muscle. In order to function as a pump the heart must contract and relax rhythmically rather than maintain contraction Skeletal muscle is equipped to sustain tension and can be tetanized but after each contraction the heart must attain a state of relaxation and remain relaxed long enough to fill with blood Cardiac muscle and particularly ventricular muscle possesses properties which tend to maintain an alternation of systole and diastole thus avoiding a sustained contraction Evidence of the operation of these factors can be determined in two ways

THE PLATEAU The transmembrane action potentials of individual cardiac cells of certain species reveal a plateau following the overshoot which indicates a retardation of repolarization and a delayed recovery of normal excitability This is particularly true in ventricular tissue of large mammals but auricular fibers of some hearts (frogs and turtles) also reveal a brief plateau in the recovery phases of the cycle The rapidly beating ventricles of birds and smaller mammals show practically no plateau Drugs and other influences which can change heart rate modify profoundly the duration of the plateau and the recovery phase of the heart cycle When the plateau is curtailed the refractory period is generally shortened and the heart becomes susceptible to greater rapidity of drive and a possible inefficiency of pumping action The presence of the

of a *particular kind trigger a regenerative process which* causes a local reversal of membrane polarity

As in nerve and skeletal muscle excitation initiates an *ionic flux* in the heart cell whereby the previously excluded Na ions enter the cell and carry the current that reverses the membrane polarity thus *producing* the upward swing of the action potential The downswing of the action potential resulting from an outward flux of K and a cessation of Na movement, however, is considerably delayed, particularly in ventricular cells There is an immediate reduction of the overshoot but a plateau phase intervenes before final rapid repolarization The cause of this plateau period is not known It appears to be peculiar to cardiac muscle and certain types of smooth muscle and presents one of the major mysteries of cardiac physiology

As a result of this local depolarization, created by an applied stimulus or by activity in the pacemaker, a sink source relationship is established which results in an electrotonic current flow This in turn touches off the physicochemical reactions of the regenerative process in adjacent membrane and thus *an impulse is conducted along the specialized and unspecialized conducting paths of the myocardium*

THE PACEMAKER

The intrinsic rhythmicity of heart muscle is *a* peculiar property possessed *by all* vertebrate cardiac muscle tissues *At least in pacemaker tissue, the intrinsic rhythmicity appears to originate in an instability* of *the cellular membrane As soon as repolarization has* been attained a gradual *progressive depolarization* occurs which reduces membrane potential to a point of instability permitting sudden reversal of membrane polarity due to a sudden increase of ionic flux Whether this breakdown should be described as caused by development of an intrinsic excitatory process or by a localized deficiency in the metabolic reactions maintaining polarization cannot as yet be decided Only tissues serving a pacemaker function show this depolarization preceding origin of the propagated response

The cells of highest intrinsic rhythmicity serve *as a pacemaker in that* impulses originating *from them sweep over the heart initiating* activity *in other elements of the myocardium* This is possible because cells recover normal excitability after each contraction well before development of their

During the refractory period stimuli can have only a localized effect although there may be a creep or gradual spread of this excitation before full normal propagation can ensue after recovery of the membrane The latency of response observed is accounted for by this confining refractoriness and the persistence of local excitatory processes Thus the refractory period is both a period of subnormal excitability and also a period of irresponsiveness but only in the sense that propagation of a normal type cannot begin until the termination of this interval and until normal polarization is attained The refractory phase of the cycle is also a period during which local reactions may persist for sufficient time to permit a change in their nature and extent before giving origin to a propagated response During the vulnerable phase of the refractory period stimulation may eventuate in fibrillation The nature of the local excitatory states created in the heart, particularly during the phase of subnormal excitability, presents a problem of significance.

Although, as stated previously there is practically no period in the cardiac cycle during which the heart is completely unaffected by stimulation it is reasonable to subdivide the post-excitation subnormal period into at least two phases Certainly multiple processes occur which eventuate in a progressive recovery of excitability and responsiveness Although the principle of subdivision is acceptable rigid criteria are lacking The terminal boundary of the relative refractory period is clearly identified by stimuli of many durations but this does not hold for the boundary of the phase of absolute refractoriness Certainly the early processes of recovery differ from those of the later phases It also appears that after a certain degree of repolarization has been attained a rather fixed sequence of events occurs which is less subject to modification than are the earlier processes Evidence can be quoted in support of this hypothesis but it is not possible at present to allocate certain processes to the absolute and others to the relative refractory period.

1) The action potentials of individual cardiac cells reveal three phases a) the initial depolarization and *overshoot*, b) the plateau and c) the phase of quick repolarization These phases vary or can be affected independently indicating that different processes are involved in various stages of recovery or at least that the quantitative relationships and balances maintained are quite dissimilar

2) The strength-duration curves obtained at various intervals in the cycle fall into three categories a) the *relatively uniform* curves obtained in all parts of diastole and in the supernormal period, b) the family of

plateau also delays the onset of any intrinsic excitatory process Neither the cause of the *plateau nor the factors responsible for its* practical disappearance under some circumstances are known It is certainly true that in paroxysmal tachycardia both the plateau and the refractory period are so short that the heart remains contracted for too long a proportion of its cycle to permit adequate filling, consequently a sufficient volume of blood cannot be ejected to maintain arterial pressure It has become quite clear that more study will be required before it can be decided *whether the plateau is due to a deficiency of the* recovery processes or to a delaying action engendered by some reaction peculiar to certain cardiac muscle It does seem that *this delay in repolarization or recovery is* an integral part of the process responsible for the fact that in cardiac muscle the duration of refractoriness coincides with the contractile processes This contrasts with the situation found in skeletal muscle where refractoriness ends prior to contraction

THE REFRACTORY OR IRRESPONSIVE PERIOD A periodic refractoriness and unresponsiveness are characteristic of certain phases of *the recovery process It has been constantly emphasized that* these terms should be employed in a relative sense A second propagated response cannot be evoked until a certain time lapse after the beginning of an initial action potential a period of relative refractoriness also follows each action potential and for a time a stimulus of threshold strength for diastole will have no detectable effect. When very strong stimuli are applied, however, it appears that the absolute refractory period is very short It *seems quite probable that in such cases the stimuli have a* persisting effect because of some abnormal or different mode of action When one considers how a stimulus might act during the refractory period to exert a sufficiently long lasting effect to initiate an action potential after reestablishment of normal ability to propagate an impulse there appear to be but two possibilities (1) When the membrane is depolarized the only mechanism left for carry over of the effects of an applied stimulus would be a localized delay *in repolarization* which, of course, could not produce a response until surrounding tissue had attained a high degree of repolarization It is conceivable that very strong stimuli may act in this manner but proof is lacking (2) Later in the refractory period a more normal form of stimulation occurs After some repolarization has taken place a stimulus could reverse this process *locally although possibly with greater* than normal difficulty because during the refractory period the processes *of recovery* are in ascendancy

During the refractory period stimuli can have only a localized effect although there may be a creep or gradual spread of this excitation before full normal propagation can ensue after recovery of the membrane. The latency of response observed is accounted for by this confining refractoriness and the persistence of local excitatory processes. Thus the refractory period is both a period of subnormal excitability and also a period of irresponsiveness but only in the sense that propagation of a normal type cannot begin until the termination of this interval and until normal polarization is attained. The refractory phase of the cycle is also a period during which local reactions may persist for sufficient time to permit a change in their nature and extent before giving origin to a propagated response. During the vulnerable phase of the refractory period stimulation may eventuate in fibrillation The nature of the local excitatory states created in the heart, particularly during the phase of subnormal excitability presents a problem of significance

Although as stated previously there is practically no period *in the* cardiac cycle during which the heart is completely unaffected by stimulation it is reasonable to subdivide the post-excitation subnormal period into at least two phases Certainly multiple processes occur which eventuate in a progressive recovery of excitability and responsiveness Although the principle of subdivision is acceptable rigid criteria are lacking The terminal boundary of the relative refractory period is clearly identified by stimuli of many durations but this does not hold for the boundary of the phase of absolute refractoriness Certainly the early processes of recovery differ from those of the later phases It also appears that after a certain degree of repolarization has been attained a rather fixed sequence of events occurs which is less subject to modification than are the earlier processes Evidence can be quoted in support of this hypothesis but it is not possible at present to allocate certain processes to the absolute and others to the relative refractory period.

1) The action potentials of *individual* cardiac cells reveal three phases a) the initial depolarization and overshoot, b) the plateau and c) the phase of quick repolarization These phases vary or can be affected independently indicating that different processes are involved in various stages of recovery or at least that the quantitative relationships and balances maintained are quite dissimilar

2) The strength duration curves obtained at various intervals in the cycle fall into three categories a) the relatively uniform curves obtained in all parts of diastole and in the supernormal period b) the family of

curves obtained late in the relative refractory period showing a gradual shift upward and to the right and c) a family of high intensity curves obtained very early in the cycle lying much above and to the right of the others (Figure 16) This observation suggests that stimuli applied early in the cycle may act by different intermediate processes

3) Impedance studies have shown that resistance is high both before initiation of the action potential and throughout the plateau phase in heart muscle It drops markedly during depolarization and possibly during the quick recovery phase only to increase again as normal polarization is attained Thus within the total refractory period there are early *and late intervals of low resistance to current flow*

4) Some of the most convincing evidence of different characteristics of early and late refractoriness comes from studies of the effects of rate temperature changes and certain drugs upon the heart. The relative refractory period is not changed but the absolute refractory period, as defined by the commonly employed stimuli, is markedly altered in each case This would be very difficult to explain without the assumption that the chemicophysical processes in these two periods are different.

5) The very strong stimuli required to produce an ultimate effect when placed very early in the cycle seem merely to have an absolute threshold requirement When this is attained they remain effective earlier *and earlier without additional strength requirement It seems as though* the tissues are merely passive and the effects of the stimulus are unrelated to recovery processes

6) Early in the relative refractory period there is absolute refractoriness to very strong stimuli but not to stimuli of moderate strength This "nothing" phenomenon can only be elicited early in the relative refractory period and not during its later phases nor during diastole.

7) Finally, during certain phases of the refractory period the heart is vulnerable to fibrillation This is sufficient evidence to support the contention that recovery is a progressive process involving numerous physicochemical changes It is less generally recognized that recovery of excitability is not a smoothly progressive process in the sense that at certain periods the heart is more susceptible to certain types of stimuli than it is later, after recovery has progressed still further

Generally speaking the action potential of heart muscle and the refractory period coincide, subnormality ends with repolarization It has been shown, however, that refractoriness is not merely a matter of complete

or partial depolarization. At low temperatures the total refractory period lasts much longer than does the transmembrane action potential Normal excitability is not restored by repolarization of the cell. An explanation of why full excitability is restored more slowly than is normal membrane polarization cannot be given but the observation does serve as evidence that intermediate reactions occur between recovery of membrane potential and the restoration of normal excitability in heart tissue

SUSCEPTIBILITY TO STIMULATION AT VARIOUS INTERVALS OF THE CYCLE

THE ACTION OF STIMULI It has been found that late in the refractory period a local excitation or response occurs under the cathodal testing electrode which persists until a normally propagated response can occur Of course a higher intensity of stimulation is required to produce this effect than is required to produce a response during diastole. Somewhat earlier in the cycle anodal current of high intensity stimulates more readily than does cathodal current flow One explanation offered is that anodal current flow is known to aid repolarization the tissue under the anode is repolarized and attains a condition permitting it to be affected by the break of the anodal current or by the current from the distant cathode. The evidence supporting this conclusion is that when anodal stimulation is compared with stimulation by means of a stigmatic cathode the anodal stimulus is more effective at a particular interval (the dip phase) of the refractory period Furthermore when bipolar stimulation is used the propagated response originates near the anode during the interval of the dip

THE "NO RESPONSE" PHENOMENON The use of very strong stimuli reveals a peculiar phenomenon Very early in the relative refractory period and also in the dip stimuli of high intensity produce no response and seem to have no effect although slightly weaker stimuli produce extrasystoles multiple extrasystoles or fibrillation. These stimuli which elicit the "nothing" phenomenon do not produce irreversible injury The tissues under the electrodes recover normal excitability as the cells repolarize.

This peculiar unresponsiveness to high strengths of stimulus has been observed to occur in both auricles and ventricles of the hearts of dogs, cats and turtles it occurs in isolated tissues also but it has only been

demonstrated during the early phases of the recovery period, never during diastole

THE "DIP" PHENOMENON Chains of reactions are involved in excitation, response and recovery During these chains of reactions there may be opportunity for irregularity of progression of recovery or for oscillation occasioned by competitive influences Whatever the cause may be, an irregularity which resembles a damped oscillation is seen in the progressive recovery of normal excitability following activation of the heart.

During the refractory period at least two dips are observed which can be described as brief periods of unsustained degrees of recovery of excitability There is also a supernormal period immediately following recovery from this refractoriness These dips are intervals in the refractory phase of the cycle during which stimuli can more easily than just before and just afterward produce a local excitatory state which will persist until a propagated impulse can be initiated

Normally there are no visible signs of oscillations or "dips" in the cellular potentials of cardiac tissue However, the positions of these dips do roughly coincide with phases of change in the membrane action potential The first or primary dip coincides with the end of the plateau when the quick phase of repolarization begins and the second or major dip coincides with the terminal phase of repolarization

VULNERABILITY One of the most significant points about these dip phenomena is *that during these intervals the heart is most vulnerable to fibrillation* Some factors such as vagus nerve stimulation, adrenaline and drugs which tend to promote fibrillation prolong the duration of the dips but their greatest effect is on the vulnerable period itself *As shown in Chapter VI, the vulnerable period overlies the dip but thresholds* for fibrillation are considerably higher than for extrasystoles Influences affecting vulnerability cause the threshold for fibrillation to approach that for extrasystoles During vagus stimulation it is sometimes difficult to find a lower threshold for extrasystoles than for fibrillation in this vulernable period

Vulnerability may be due to asynchronous states of fiber excitability and conductivity It may be due to the fact that a period of relative hyper excitability is followed by a period of regression which serves to disorganize and fractionate the response There may be an instability of the membrane which facilitates repetitive firing at these intervals of vulnerability The statement that can be made with certainty is that during the vulnerable

period conditions maintain which potentiate disorganization of action of heart elements and escape from the integrating influence of the pacemaker The nature of this state and the cause of this vulnerability is not under stood.

FIBRILLATION

Fibrillation usually results from dissociation of activity in various elements of the myocardium This dissociation is po sible because these individual elements possess the ability to initiate their own activity or to respond individually to applied stimuli It has been found however, that this property of independence of activity is also possessed by segments of individual cardiac fibers and in the most extreme degrees of disorgan ization even individual cells do not behave as units Whatever the intrinsic activating force may be which causes rhythmic activity of cardiac tis ue it appears to be possessed by all portions of the membrane.

It is our opinion that flutter and fibrillation cannot be considered to be invariably due either to a simple fixed circus movement or to activity of multiple independent pacemakers Fibrillation originates in and is maintained by interaction reentry is involved and this may be due to return of an impulse to a previous segment of muscle after it has followed an irregular path or to escape of intrinsic excitatory processes from domi nation by normal pacemakers Electrotonic current flow should be con sidered to play a very important role in promoting these arrhythmias It is thought that the eddy currents generated by activity in one region may touch off activity in adjacent tissues either by initiating a regenerative process there or by summating with locally developing excitatory pro cesses These eddy currents would act primarily on nearby cells possessing at the moment the lowest thresholds Activity could thus proceed stepwi e or in a saltatory manner over the heart in a random but repetitious fashion This concept incorporates the essence of both the circus movement theory which is reentry from per isting activity and the multiple focus theory which employs the concept of multiple foci of newly initiated activity At the same time it employs the known excitatory action of current flow surrounding an active or depolarized area The well known phenomena of nerve fiber interaction which permits impulses to jump barriers and which affects speed of conduction in parallel muscle and nerve fibers should be incorporated into the consideration of the mechanism operating in fibril latory activity and in the etiology of other related arrhythmias

DRUG ACTION ON ARRHYTHMIAS 1) *Fibrillatory action* Evidence

has likewise been produced to the effect that fibrillation does not result from a single type of abnormality such as shortened refractoriness and slowed conduction Disorganization can be brought on by imbalance originating from a number of effects This is well illustrated by the fibrillation produced as a result of excessive doses of some antifibrillatory agents Prolongation of refractoriness may tend to prevent fibrillation but excessive prolongation which causes imbalance with other changes in the heart predisposes toward fibrillation The converse generalization can also be made, that drugs such as acetylcholine, adrenaline and many others which tend to promote fibrillation can also act to abolish the arrhythmia There tends to be a reversal of the effects of the quick acting drugs such as epinephrine and acetylcholine and even of vagus action for that matter This duality of effect has not been studied intensively enough to determine whether the fibrillatory and antifibrillatory actions of these drugs are related to one or the other phases of their dual effect. Some correlation has been attempted in the case of epinephrine and norepinephrine and it has been found that fibrillation is most easily produced at a time when these drugs are having an excitatory action, but studies of this nature have not been undertaken with other drugs

2) *Antifibrillatory action* Antifibrillatory drugs do not abolish the dip phenomenon The drugs studied do affect excitability, tending to raise the threshold and prolong the refractory period, but have little effect on conduction at therapeutic levels

Changes in threshold and refractoriness are not invariably proportional to the antifibrillatory effect of a specific drug or dosage It appears that factors other than threshold excitability and duration of refractoriness are of importance to the production and prevention of fibrillation It has been found that the antifibrillatory drugs stabilize the membrane in that they tend to prevent change in transmembrane potential by applied stimuli but do not modify either resting potentials or action potentials

Drugs are spoken of as antifibrillatory because they tend to protect the heart from fibrillation rather than because of any ability to abolish the arrhythmia once it has begun These drugs raise the threshold for fibrillation and reduce the duration of the vulnerable periods Quinidine, procaine and certain other of the antifibrillatory agents will change auricular fibrillation to auricular flutter or may even abolish the arrhythmia altogether, but in the case of ventricular fibrillation there is very little opportunity for the drug to penetrate that organ s thick muscular wall

in the absence of a coronary circulation during fibrillation and this alone would prevent the stoppage of ventricular fibrillation by an administered drug

The drugs which are classified as antifibrillatory agents have a depressant action on the heart. As such they oppose the fibrillatory action of electric stimuli anesthetics, adrenaline, etc They might likewise reduce a dangerous gradient between hyperactive or normally irritable tissue and depressed segments of the heart but since fibrillation can result from imbalance due to depressed function administration of a depressant drug is contraindicated in certain instances. Certainly the rationale of the situation indicates that since fibrillation does not originate from any one condition it is not reasonable to search for one drug to counteract all conditions which might eventuate in fibrillation Until more can be learned concerning the basic processes in cardiac cell function and the mechanism of fibrillation search for new antifibrillatory agents and the use of known drugs will have to be carried on in a more or less empirical fashion

DEFIBRILLATION If fibrillation is due to shortened refractoriness and slowed conduction a drug which would either accelerate conduction or prolong refractoriness should be beneficial. Quinidine does prolong refractoriness If fibrillation and flutter are due to ectopic foci of beat origin any influence which would suppress the intrinsic excitatory process should defibrillate the heart. Vagal stimulation which does suppress beat origin does often abolish auricular fibrillation Matters are not always this simple, however, and it appears that many methods of defibrillation such as *heating* and cooling may work, but all too infrequently to be of much practical use Potassium chloride will stop cardiac cell activity in fibrillating hearts and if calcium chloride is then given normal rhythms can be restored. This procedure greatly weakens the heart and is a hazardous undertaking always requiring cardiac massage to aid in reestablishment of function.

Only *one* method is at all reliable and that is electric countershock. Employment of this method is based upon the principle that a complete stoppage of activity in heart cells does give opportunity for the normal pacemakers to assert their dominance and their unifying control of cardiac reactions.

Electric countershock can attain this end more safely than any other method due to the fact that cardiac cells can be dominated by high

intensity shocks at practically any time in their cycle and a uniformity of condition established Following termination of the defibrillating current the cells presumably repolarize and come under the control of the pace maker which fires the earliest impulse Countershock if properly applied has no untoward after effects Normal pacemaker tissue may not take over control of the heart immediately and thus the use of driving stimuli or massage may be required Defibrillation through a closed chest can be successfully accomplished Further developments in this field are to be anticipated Defibrillatory and cardiac drive apparatus for use in case of cardiac arrest are now available but both of these procedures are still attended by many hazards and many uncertainties of result.

MECHANICAL ACTION OF HEART MUSCLE

The phases of mechanical action in the cardiac cycle can be correlated with the excitability cycle and the changes in potential associated with depolarization and repolarization of the heart

Methods of recording mechanical actions are such that a lesser degree of precision can be attained than in the timing and recording of the electrical signs of cell membrane responses The primary dip corresponds to the earliest phase of the relaxation process and the second or major dip occurs later in the declining phase of systole Vulnerability is thus associated with the terminal stages of relaxation

The contractile processes of heart muscle are intimately related to membrane activity Stimuli falling in the refractory period however, can produce a propagated electrical response unassociated with any record able mechanical response The membrane response can, under certain circumstances become dissociated from activity of the contractile elements of the cardiac cell Similarly contraction of actomyosin has been produced in the absence of an excitable membrane

It has been demonstrated that the small amplitude of early extrasystoles is not entirely due to lack of filling of the heart. The contractile elements are just not able to develop normal tensions Recovery of this ability requires a longer time than does the process of membrane repolarization

Although stimulation of a beating heart early in the refractory period may evoke a normal propagated electrical response unassociated with a detectable response of the contractile tissue this membrane response is not without effect upon the contractile elements of the cell The next expected beat shows an enormous augmentation as does the second, third

and even the fourth subsequent contraction The propagated electrical response though unable to evoke an immediate shortening nevertheless modifies the ability of the contractile tissue to develop tension This is not a phenomenon of extra filling becau e it occurs in isolated strips. It presents another problem for study by those interested in finding an explanation for the phenomena which determine the intensity and nature of the mechanical action of heart muscle

The phenomena of cardiac activity and response can be placed in two categories 1) those such as intrinsic rhythmicity of action, excitability, the ability to propagate an impulse refractoriness etc. are dependent upon membrane function 2) those involving fiber shortening pumping action, the build up of tension treppe, etc. involve activity of the con tractile elements of the heart cell. Activity of the membrane and the contractile elements is generally linked but can be semi independent. The nature of this linkage is not known but the phenomenon is certainly worthy of further consideration.

Thus many aspects of cardiac function and many of the basic processes of heart muscle activity require further study but recent advances in instru mentation have been such that problems of a major magnitude can now be approached with some confidence. Apparatus and methods are avail able for the continuation of productive investigations

The contributions of this laboratory to the study of cardiac irritability have been described here. A description of the apparatus used has been given Methods employed in this investigation and results obtained have been described. It is our hope that we have hereby assisted progress in this important field of medicine and physiology We trust that those who read this monograph may acquire helpful information and have many suggestions and questions to propose. We are confident that some of these will eventually return to us and be of assistance in our future undertakings.

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